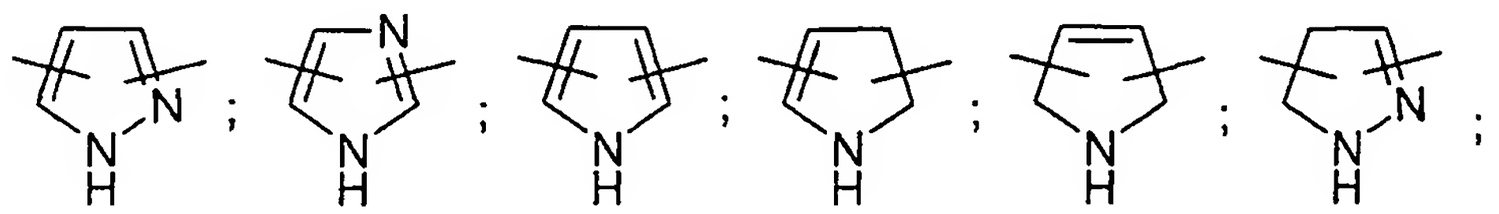
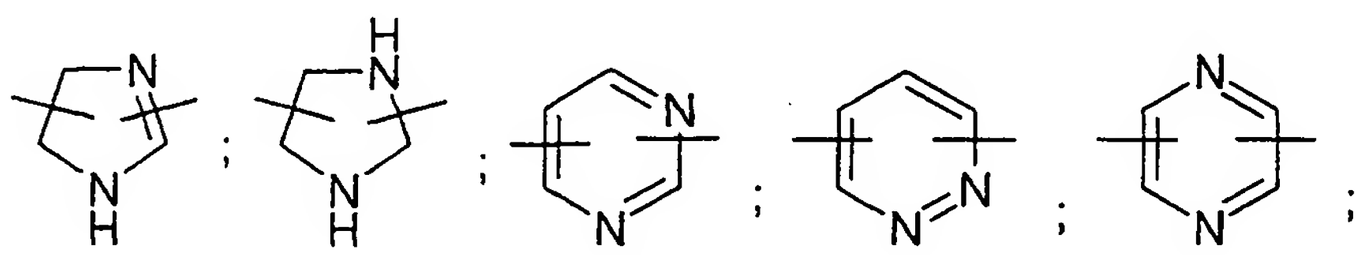
ductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethylalcohol, coniferyl alcohol, allopurinol;

- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid.

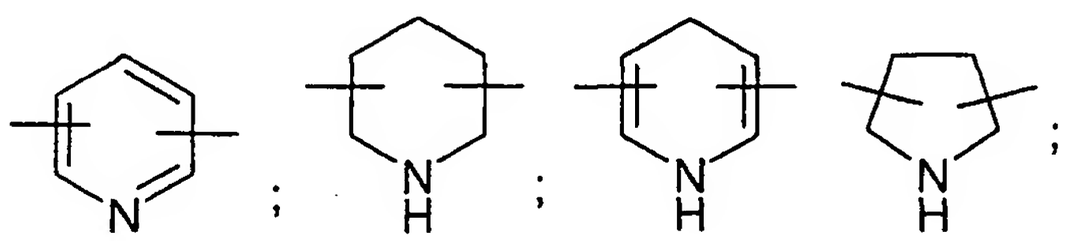
5. Use according to claims 1-4, wherein Y^3 in formula (III) is selected from the following:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



(Y7) (Y8) (Y9) (Y10) (Y11)



(Y12) (Y13) (Y14) (Y15)

6. Use according to claim 5, wherein Y^3 is an aromatic ring having 6 atoms, containing one nitrogen atom and having the two free valences respectively in position 2 and 6.

7. Use according to claims 6, wherein Y^3 is Y12 (pyridyl) substituted in position 2 and 6 or having the two bonds also in asymmetric position.

8. Use according to claims 1-7, wherein the precursors of B of formula (I) for the synthesis of the nitrooxyderivatives usable in the present invention are the following: ferulic acid, N-acetylcysteine, cysteine, caffeic acid, hydrocaffeic and gentisic acid; and the precursor drugs of R are the following: ibuprofen, flurbiprofen, naproxen, ferulic acid.

9. Use according to claims 1-8, wherein the compounds of formula (I) are the following:

- [1,1'-biphenyl]-4-acetic acid-, 2-fluoro-alpha-methyl-, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxo-1-propenyl]phenylester (XII);
- alpha-methyl-4-(2-methylpropyl) benzenacetic acid-, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxo-1-propenyl]phenylester (XIII);
- 6-methoxy-alpha-methyl-2-naphthalenacetic acid-, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxo-1-propenyl] phenylester (XIV);
- (S)-N-acetylcysteine-4-(nitrooxy)butylester-, (S)-6-methoxy-alpha-methyl-2-naphthalenacetate (XV);
- (S)-N-acetylcysteine-4-(nitrooxy)butylester-, 2-fluoro-alpha-methyl-[1,1-biphenyl]-4-acetate (XVI);
- (S)-N-acetylcysteine-4-(nitrooxy)butylester-, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetate (XVII);
- (S)-N-acetylcysteine-4-(nitrooxy)butylester-, alpha-methyl-4-(2-methylpropyl)benzeneacetate (XVIII);
- 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid-, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxo-1-propenyl]

phenylester (XIX);

- (S)-N-acetylcysteine-4-(nitrooxy)butylester-, 2-[(2,6-dichlorophenyl)amino]benzeneacetate (XX);
- trans-3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid-, 4-(nitrooxy)butyl ester (XXI);
- trans 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid-, 3-(nitrooxymethyl)phenyl ester (XXII);
- trans 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid-, 6-(nitrooxymethyl)-2-pyridinylmethyl ester hydrocloride (XXIII);
- 2-fluoro-alpha-methyl-[1,1'-biphenyl]-4-acetic acid (nitrooxy butyl)ester (XXX);
- (S)-N-acetylcysteine-4-(nitrooxy)butylester-, trans-3-(4-hydroxy-3-methoxyphenyl)-2-propenoate (XXIV);
- trans-3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid-, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxo-1-propenyl]phenylester (XXV).

10. Use according to claims 1-9, wherein if the compounds of formula (I) have one or more chiral centres, they are used in racemic form or as mixtures of diastereoisomers, as single enantiomers or single diastereoisomers; if they show geometric asymmetry, the compounds in the cis or trans form are used.
11. Use according to claims 1-10, wherein the compounds of formula (I) are used in combination with one or more vaccines.
12. Mixtures of compounds as defined in claim 11.
13. Compounds according to claim 9, selected from:
    - trans 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic

acid-, 4-(nitrooxy)butyl ester (XXI);

- trans 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid-, 3-(nitrooxymethyl)phenyl ester (XXII);

- trans 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid-, 6-(nitrooxymethyl)-2-pyridinylmethyl ester hydrocloride (XXIII);

- (S)-N-acetylcysteine-4-(nitrooxy)butylester-, trans-3-(4-hydroxy-3-methoxyphenyl)-2-propenoate (XXIV);

- trans-3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid-, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxo-1-propenyl]phenylester (XXV).

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WO 02/053188 A1

(54) Title: COMPOSITIONS COMPRISING CYCLODEXTRINS AND NO-RELEASING DRUGS

(57) Abstract: The present invention relates to composition comprising cyclodextrins and a NO-releasing drug of formula, A-X-L-NO_n, wherein A is the radical deriving from a drug; X is a divalent radical connecting A with the NO-releasing group L-NO_n; L is selected from the group consisting of: O and S; n is 1 or 2.

Compositions comprising cyclodextrins and NO-releasing drugs

Field of the Invention

The present invention relates to compositions comprising a NO-releasing derivative of a pharmaceutically active compound.

Background of the Invention

In the last decade there has been a growing interest towards the preparation and the properties of compounds comprising a radical derived from a compound having pharmaceutical activity and a NO releasing group.

EP 670 82, EP 759 899 and EP 722 434 disclose nitric esters of non-steroidal antiinflammatory drugs (NSAIDs). These compounds present an improved activity and reduced side effects when compared to the drug without NO-releasing group.

WO 98/15568 discloses nitrate esters of corticoids. Also in this case a reduced toxicity is observed when the nitrate group is present.

Compounds comprising a radical derived from an antithrombotic drug and a NO-releasing group are described in WO 98/21193. The comparative data show that the introduction of the NO-releasing group causes an increase of activity of the drug.

WO 00/61537 discloses the preparation of drugs comprising a NO releasing group linked to, inter alia, anti-inflammatory, analgesic, bronchodilators, ACE-inhibitors, β-blockers, antineoplastic compounds. The use of a linking group presenting specific antioxidant properties allows the use of these drugs to patients affected by oxidative stress and/or endothelial dysfunction.

Thus, it is possible to say that the introduction of NO releasing groups has proven to be advantageous in many classes of drugs. However, the introduction of a NO releasing group often leads to a relevant drawback, i.e. a significant reduction in water solubility, that might lead to a slower adsorption rate of the drug in the human body. It is therefore desirable to find methods to improve the bioavailability of compounds comprising a radical derived from a compound having pharmaceutical activity and a NO-releasing group.

The use of cyclodextrin complexes in combination with NO releasing compounds is known from WO 95/29172. In that case, however, there was no radical derived from a compound having pharmaceutical activity in the molecule complexed with Cyclodextrin and, furthermore, the problem was to render the molecule stable to degradation. Thus, both the

type of compound and the technical problem solved by the patent application are quite different from the present case.

Summary of the invention

The present invention relates to compositions for pharmaceutical use comprising a cyclodextrin and a compound comprising a radical derived from a compound having pharmaceutical activity and a NO releasing group.

Detailed description of the invention

The invention relates to compositions comprising cyclodextrins and a NO-releasing drug of formula

$$A\text{-}X\text{-}L\text{-}NO_n$$

wherein **A** is the radical deriving from a drug;

X is a divalent radical connecting A with the NO-releasing group;

L is selected from the group consisting of: O and S; preferably it is O;

n is 1 or 2, preferably it is 2.

The syntheses of these compounds is described in the following patents, which are herewith incorporated by reference: US 5,861,426, WO 98/15568, US 5,621,000, WO 00/61537, WO 00/61541, WO 00/61604, US 5,703,073, US 6,043,233, US 6,057,347.

Cyclodextrins are cyclic oligosaccharides constituted by the union of from 6 to 12 glucose units through α(1,4) bonds. The word CD, used to indicate them, is usually preceded by a Greek letter that indicates the amount of glucose units (α corresponds to 6, β corresponds to 7, and so on).

A characteristic parameter of CDs is the diameter of the cavity wherein the compound is complexed.

For many purposes α-CD have a too small cavity (5 Å) to complex molecules of a medium size. This is why for many applications β-CD is preferred (diameter: 6 Å). The drawback of β-CD is its low solubility in water (18.5 g/l). To overcome the problem, probably caused by inter- and intramolecular hydrogen bonds between the hydroxyl groups, β CD derivatives have been prepared which present a considerably higher water solubility. In fact, it is known that the hydroxyl groups in the glucose units of CDs can be selectively reacted to prepare ethers, esters, ionic ethers (see for example the review "Physicochemical Characteristics and Pharmaceutical uses of Cyclodextrin Derivatives" D. Duchene et al., Pharmacueutical Technology International, June 1990).

The cyclodextrins to be used in combination with the compounds of formula A-X-L-NO_n are not particularly limited. Preferred examples of cyclodextrins useful in the present invention are: α-CD, dimethyl α-CD, trimethyl α-CD, β-CD, dimethyl β-CD, trimethyl β-CD, 2-hydroxypropyl β-CD, 3-hydroxypropyl β-CD, 2,3-dihydroxypropyl β-CD, γ-CD, dimethyl γ-CD, trimethyl γ-CD and polymeric CD.

In each particular case, it is possible to determine, with a few trials, which one is the most suitable cyclodextrin to be used in combination with a specific drug.

The molar ratio between the drug and the cyclodextrin can vary in a broad range. Preferably it is comprised between 1:10 and 10:1, more preferably between 3:1 and 1:3.

The composition according to the invention can be prepared in different ways. For example, it is possible to mix together the cyclodextrin and the NO-releasing drug in water. Due to the low solubility of most drugs, the drug is partly or fully dissolved when complexed with the CD. The solution is then dried and the solid recovered. It is also possible to use a cosolvent (e.g. ethanol) which is miscible with water and that solubilizes the drug. In another embodiment it is also possible to isolate the pure complex by using a two phase system: a lipophilic solvent wherein the drug is soluble, and water. The CD dissolves in the water phase, the drug in the lipophilic pahse. The complex CD-drug is formed at the interphase. If it is soluble in water, it is recovered from the water phase.

Finally, it is also possible to simply mix the drug and the CD in the solid state by using mixing and/or milling means well known in the art.

In a preferred embodiment, the drug used in the compositions according to the present invention, is selected from the following classes of compounds:

non steroidal antiinflammatory and analgesic drugs, antibacterial (antibiotics), antiviral, steroids, antineoplastic, β-adrenergics (agonists and blockers), antihyperlipoproteinemic, bone resorption inhibitors.

Non limiting examples of non-steroidal anti-inflammatory and analgesic drugs are:

Aspirin, Salicylic acid, Mesalamine, Acetylsalicylsalicylic acid, Paracetamol, Etodolac, Pirazolac, Tolmetin, Bromefenac, Fenbufen, Mofezolac, Diclofenac, Pemedolac, Sulindac, Ketorolac, Indomethacin, Suprofen, Ketoprofen, Tiaprofenic acid, Fenoprofen, Indoprofen, Carprofen, Naproxen, Loxoprofen, Ibuprofen, Pranoprofen, Bermoprofen, CS-670, Zaltoprofen, Tenoxicam, Piroxicam, Meloxicam, Tenidap, Aceclofenac, Acemetacin, 5-amino-acetylsalicylic acid, Alclofenac, Alminoprofen, Amfenac, Bendazac, α-bisabolol,

Bromosaligenin, Bucloxic acid, Butibufen, Cinmetacin, Clidanac, Clopirac, Diflunisal, Ditazol, Enfenamic acid, Etofenamate, Felbinac, Fenclozic acid, Fendosal, Fentiazac, Fepradinol, Flufenamic acid, Flunixin, Flunoxaprofen, Flurbiprofen, Glucametacin, Glycol salicilate, Ibuproxam, Isofezolac, Isoxepac, Isoxicam, Lornoxicam, Meclofenamic acid, Mefenamic acid, Metiazinic acid, Niflunic acid, Oxaceprol, Oxaprozin, Oxyphenbutazone, Parsalmide, Perisoxal, Olsalazine, Pirprofen, Protizinic acid, Salacetamide, Salicilamide O-acetic acid, Salsalate, Suxibuzone, Tiaramide, Tinoridine, Tolfenamic acid, Tropesin, Xenbucin, Ximoprofen, Zomepirac, Tomoxiprol.

Non limiting examples of antibacterials (antibiotics) are:

Metronidazolo, Ethambutol, Cycloserina, Cloxyquin, Negamycin, Nitroxoline, Mupirocin, Myxin, Novobiocin, Spectinomycin, Sulbactam, Tigemonam, Tubercidin, Nifurpirinol, Nifurprazine, Glyconiazide, Isoniazide, Opiniazide, Clofazamine, Meclocycline, Minocycline, Sancicline, Tetracicline, Oxytretracycline, Chlortetracycline, Demeclocycline, Methacycline, Doxicycline, Clomocycline, Cinoxacin, Rolitetraciclyne, Pipaciclyne, Guamecycline, Lymecyclinem, Apiciclyne, Nalidixic acid, Cyprofloxacin, Enoxacin, Floroxacin, Pipemidic acid, Difloxacin, Perfloxacin, Enrofloxacin Nadifloxacin, Grepafloxacin, Lomefloxacin, Sparfloxacin, Clinafloxacin, Tosufloxacin, Trovafloxacin, Ofloxacin, Flumequine, Pazufloxacin, Rufloxacin, Norfloxacin, Cefroxadine, Cephradine, Cefaclor, Cefadroxil, Cefprozil Cefatrizine, Cefpiramide, Cephalexin, Cephaloglycin, Loracarbef, Pivcephalexin, Cephamandole, Moxalactam, Cefclidin, Cefepime, Cefuzopran, Ceftibuten, Cefpodoxime Proxetil, Cefotaxime, Cefcapene Pivoxil, Cefodizime, Ceftiofur, Ceftriaxone, Cefditoren, Cefmenoxime, Cefteram, Cefuzonam, Cefdinir, Cefetamet, Cefixime, Cefpirome, Ceftazidine, Cefminox, Cephalosporin, Cefotiam, Ceforanide, Cefazolin, Ceftizoxime, Cefazedone, Cefonicid, Ceftezole, Cephacetrile, Cephapirin, Fenbenicillin, Hetacillin, Quinacillin, Pivampicillin, Aspoxicillin, Mezlocillin, Amoxicillin, Ampicillin, Epicillin, Phenethamate Cyclacillin, Amdinocillin, Penicillin N, Apalcillin, Bacampicillin, Sultamicillin, Talampicillin, Lenampicillin, Benzyl penicillic acid, Carbenecillin, Carindacillin, Clometocillin, Cloxacillin, Dicloxacillin, Floxacillin, Metampicillin, Methicillin, Oxacillin, Penicillin O, Penicillin V, Pheneticillin, Piperacillin, Propicillin, Sulbenicillin, Ticarcillin, Meropenem, Panipenem, Imipenem, Aztreonam, Carumonan, Sulfabenzamide, Sulfacetamide, Sulfachloropyridazine, Sulfacytine, Sulfadiazine, 4'-(Methylsulfamoyl)sulfanilanilide, Sulfadicramide, Sulfadoxine, Sulfamethoxine,

Sulfaethidolo, Sulfaguanole, Sulfalene, Sulfamerazine, Sulfameter, Sulfamethazine, Sulfamethizolo, Sulfamethonide, Sulfamethoxazole, Sulfamethoxypyridazine, Sulfamethylthiazole, Sulfametrole, Sulfamoxolo, Sulfanilamide, N^4-Sulfanilylsulfanilamide, Sulfanilyurea, N-Sulfanil-3,4-xylamide, Sulfaperine, Sulfaphenazole, Sulfaproxyline, Sulfapyrazine, Sulfapyridine, 4-Sulfanilamido salicylic acid, Sulfasomizole, Sulfasymazine, Sulfathiazole, Sulfathiourea, Sulfisomidine, Sulfisoxazole, Acetyl sulfamethoxypyrazine, Sulfaguanidine, Mafenide, Succisulfone, p-Sulfanylbenzylamine, Dapsone, Acediasulfone, Thiazolsulfone, 2-p-Sulfanilylanilino-ethanol, Benzylsulfamide, p-Aminosalicylic acid, p-Aminosalicylic acid hydrazide, Phenyl aminosalicylate, 4-4'-sulfinyldianiline, Clindamycin, Lincomycin, Josamycin, Midecamycins, Rokitamycin, Spiramycins, Mikamycin B, Rosaramycin, Azithromycin, Clarithromycin, Erytromycin, Dirithromycin, Amikacin, Arbekacin, Dibekacin, Tobramycin, Dihydrostreptomycin, Streptomycin, Deoxydihydrostreptomycin, Trospectomycin, Spectinomycin, Micronomicin, Netilmicin, Apramycin, Sisomicin, Neomycin, Paromomycin, Ribostamycin, Rifampin, Rifapentine. Sulfachrysoidine, Sulfamidochrysoidine, Salazosulfadimidine.

Non limiting examples of antiviral drugs are:

Acyclovir, Amantadine, Cidofovir, Cytarabine, Didanosine, Dideoxyadenosine, Edoxuridine, Famciclovir, Floxuridine, Ganciclovir, Idoxuridine, Indanavir, Lamivudine, Kethoxal, MADU, Penciclovir, Ribavirin, Sorivudine, Stavudine, Trifluridine, Valacyclovir, Vidarabine, Xenazoic acid, Zaltacitabine, Zidovudine.

Non limiting examples of steroids are:

Budesonide, Hydrocortisone, Aclomethasone, Algestone, Beclomethasone, Betamethasone, Chlorprednisone, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone, Diflucortolone, Difluprednate, Fluazacort, Flucoronide, Flumethasone, Flunisolide, Fluocinolone acetonide, Flucinonide, Fluocortin butyl, Fluocortolone, Fluorometholone, Fluperolone acetate, Fluprednilene acetate, Fluprednisolone, Flurandrenolide, Formocortal, Halcinonide, Halobetasol propionate, Halomatasone, Halopredone acetate, Hydrocortamate, Loteprednol etabonate, Medrysone, Meprednisone, Methylprednisolone, Mometasone furoate, Paramethasone, Prednicarbate, Prednisone, Prednisolone 21-diethylaminoacetate, Prednisolone sodium phosphate, Prednival, Prednylidene, Rimexolone, Triamcinolone,

Triamcinolone acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone propionate, Mazipredone, Tixocortol, Triamcinolone hexacetonide, Ursodeoxycholic acid, Chenodeoxycholic, Mytatrienediol, Ethynil Estradiol, Estradiol, Mestranol.

Non limiting examples of antitumoral drugs are:

Antacitabine, Anthramycin, Azacitidine, 6-Azauridine, Carubicin, Chlorambucil, Chlorozotocin, Cytarabine, Daunomicin, Defosfamide, Denopterin, Doxifluridine, Doxorubicin, Droloxifene, Edatrexate, Eflornithine, Enocitabine, Epirubicin, Epitiostanol, Etanidazole, Etoposide, Fenretinide, Fludarabine, Fluorouracil, Gemcitabine, Hexestrol, Idarubicin, Lonidamine, Melphalan, 6-mercaptopurine, Methotrexate, Mitoxantrone, Mycophenolic acid, Pentostatin, Pirarubicin, Piritexim, Podophyllic acid, Puromycin, Retinoic acid, Roquinimex, Streptonigrin, Teniposide, Tenuazonic acid, Thiamiprine, Thioguanine, Tomudex, Topotecan, Trimetrexate, Tubercidin, Ubenimex, Zorubicin.

Non limiting examples of β-adrenergic compounds are:

Albuterol, Bambuterol, Bitoterol, Carbuterol, Clenbuterol, Chlorprenalina, Dioxethedrine, Ephedrine, Epinephrine, Etafredine, Ethylnorepinephrine, Fenoterol, Isoetharine, Isoprotenerol, Mabuterol, Metaproterenol, Pirbuterol, Salmeterol, Soterenol, Terbutalina, Tuloterol, Procaterol, Bufetalol, Acebutolol, Alprenolol, Arotinolol, Atenolol, Betaxolol, Bevantolo, Bucumolol, bufuralol, Bunitrolol, Bupranolol, Carazolol, Carteolol, Celiprolol, Epanolol, Indenolol, Mepindolol, Metoprolol, Nadolol, Nifenalol, Penbutolol, Pindolol, Pronethalol, Propanolol, Sotalol, Timolol, Toliprolol, Butofilol, Cervedilol, Cetamolol, Dilevalol, Esmolol, Labetalol, Metipranolol, Moprolol, Nebivolol, Oxprenolol, Practolol, Sulfinalol, Tertatolol, Tilisolol, Xibenolol, Eprozinol, Etophylline, Exoprenaline, Propoxyphilline, Reproterol, Rimiterol, 1-Teobrominacetic acid, Tetroquinol, Nadoxolol.

Non limiting examples of antihyperlipoproteinemic compounds are:

Atovarstatin, Cilastatin, Dermostatin A, Dermostatin B, Fluvastatin, Lovastatin, Mevastatin, Nystatin A_1, Pentostatin, Pepstatin, Sinvastatin

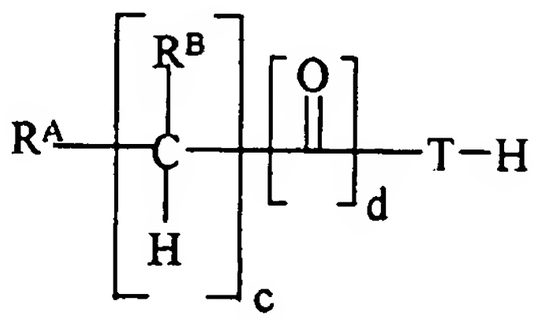
Non limiting examples of bone resorption inhibitors are:

Alendronic acid, Butedronic acid, Etidronic acid, Oxidronic acid, Pamidronic acid, Risedronic acid.

The chemical formula of the above listed compounds is reported on the Merck Index, Twelfth Edition.

Preferred drugs useful in the present invention are selected form the following formulas:

i)

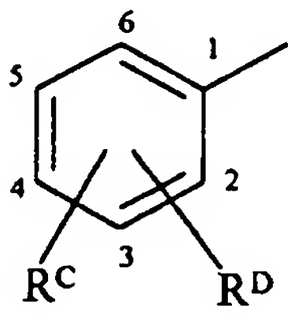


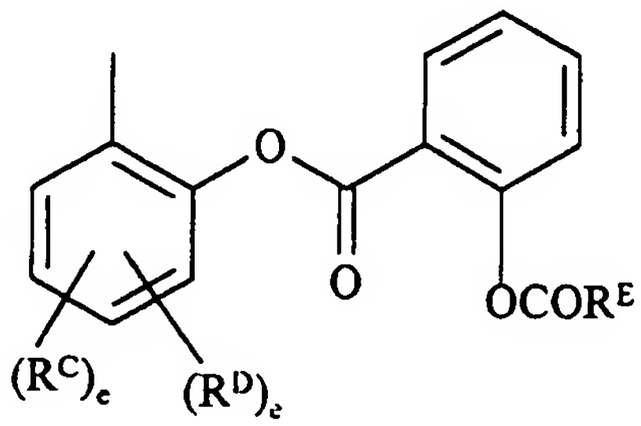
where **c** and **d** are independently 0 or 1;

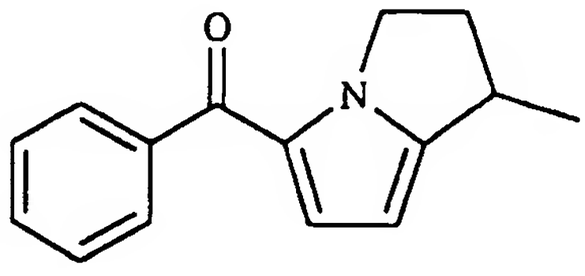
T is selected from the group consisting of: O, NH and S;

$\mathbf{R^B}$ is selected from the group consisting of H, a linear or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl; preferably R^B is H, an alkyl having from 1 to 4 carbon atoms, most preferably R^B is CH_3

When **c** is equal to 0 , **d** is 1, $\mathbf{R^A}$ is selected from the group consisting of:







wherein:

$\mathbf{R^C}$ is selected from the group consisting of amino, R^ECONH-, $OCOR^E$ group, and the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently selected from the group consisting of O, N, and S;

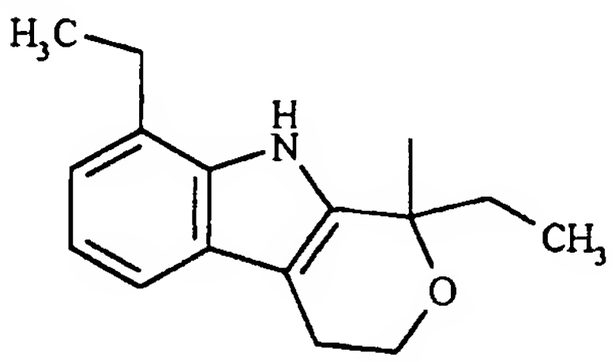
$\mathbf{R^E}$ is selected from the group consisting of methyl, ethyl and a linear or branched C_3-C_5 alkyl;

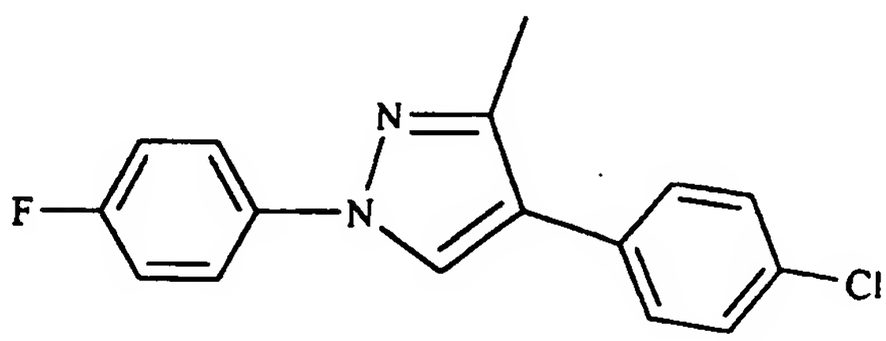
$\mathbf{R^D}$ is H, OH, halogen, a linear or when permissible branched alkyl having 1 to 4 atoms, a linear or when permissible branched alkoxyl having 1 to 4 atoms, a linear or when permissible

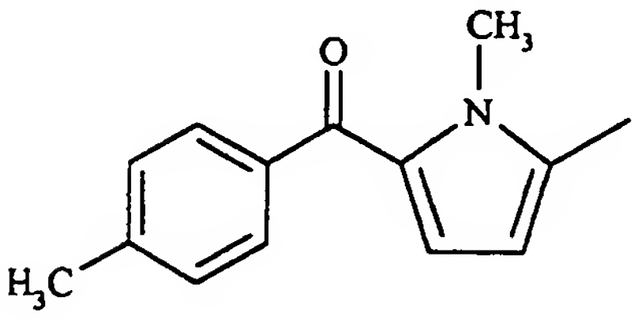
branched perfluoroalkyl having 1 to 4 carbon atoms, for example trifluoromethyl, amino, mono- or di-(C_1-C_4) alkylamino;

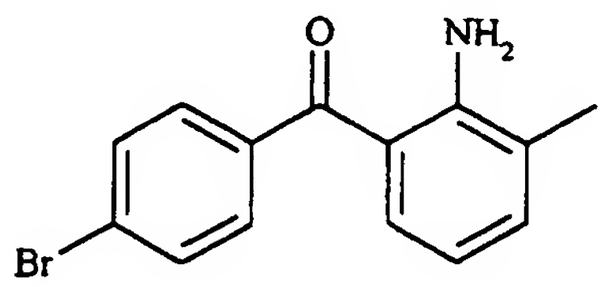
e is 0 or 1;

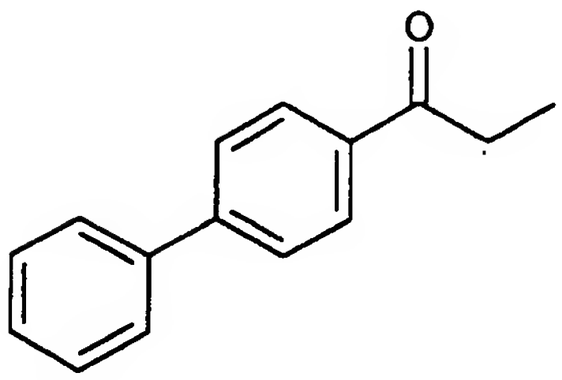
when **c** is equal to 1, **d** is equal to 1, $\mathbf{R^B}$ is hydrogen, $\mathbf{R^A}$ is selected from the group consisting of:

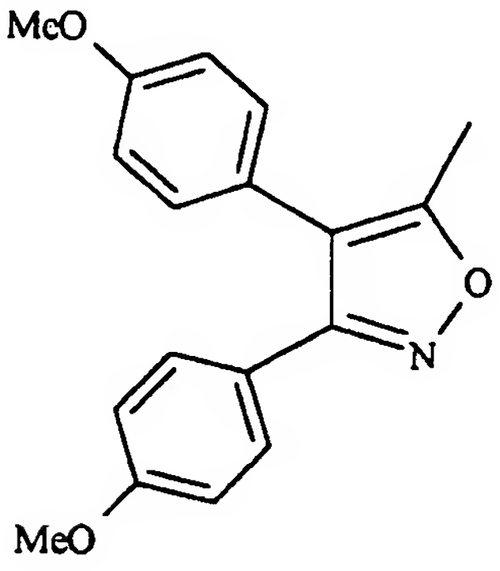


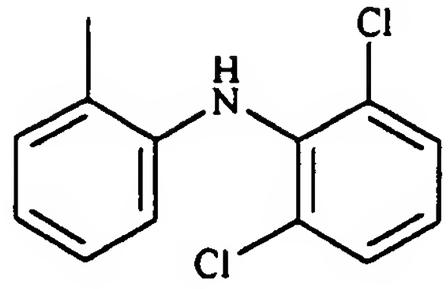


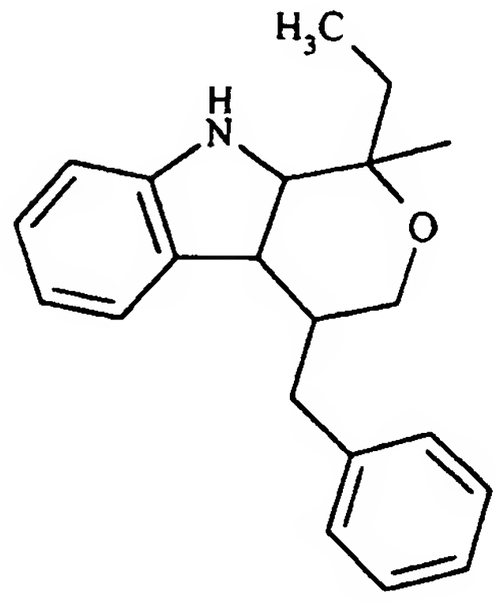


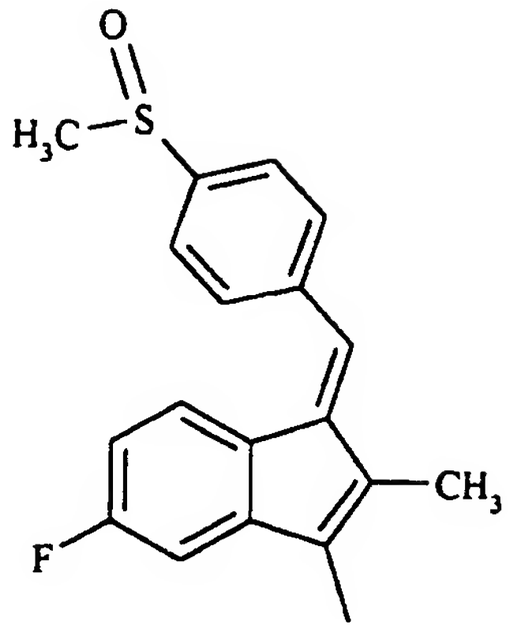


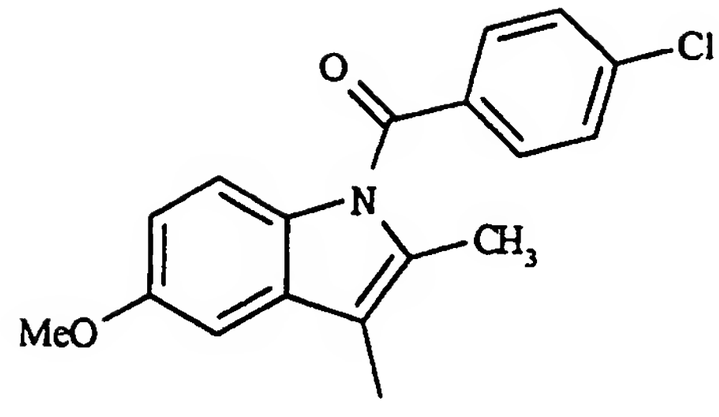




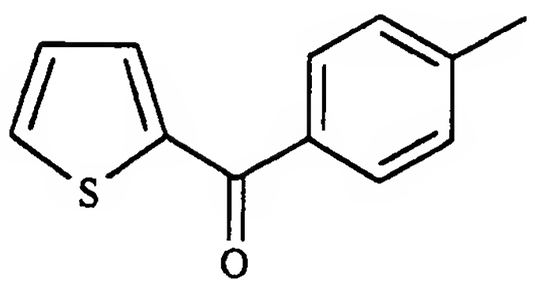


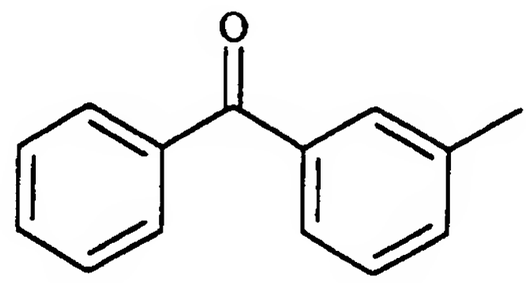


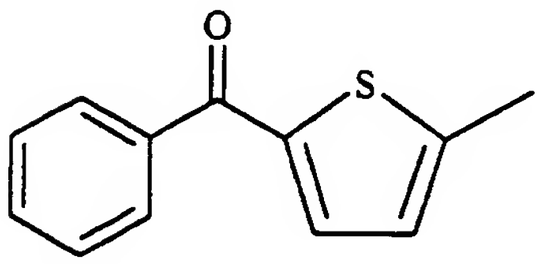


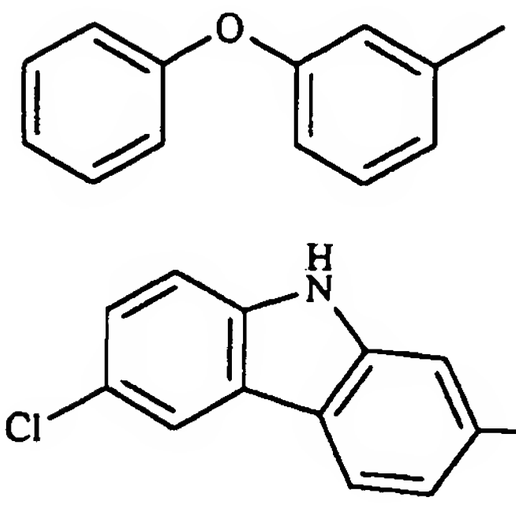


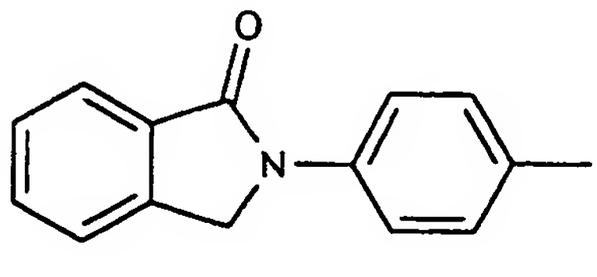
when **c** is equal to 1, **d** is equal to 1 and $\mathbf{R}^B$ is CH_3, $\mathbf{R}^A$ is selected from the group consisting of:

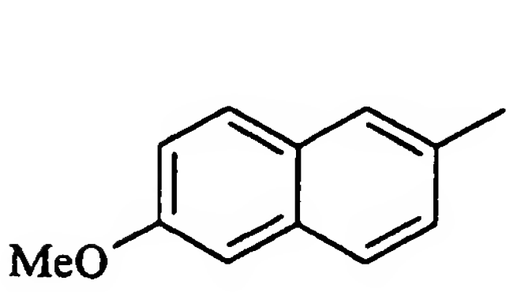


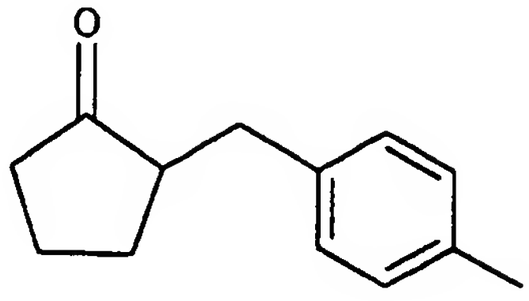


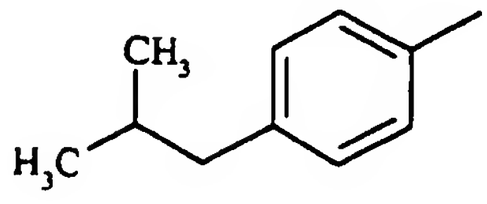


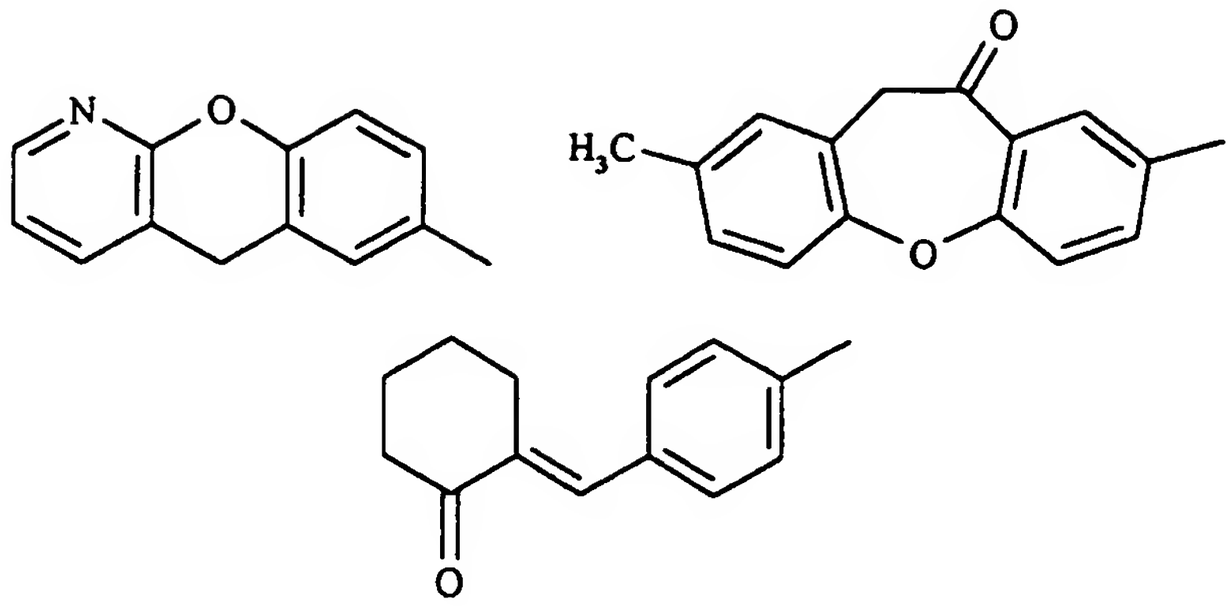


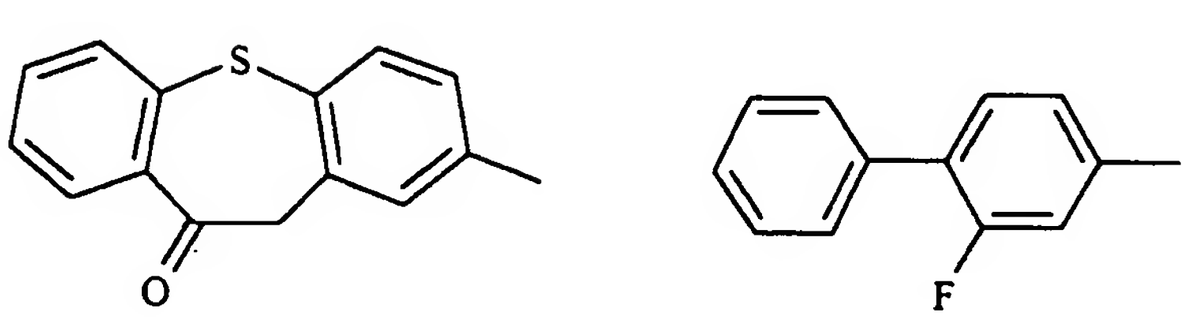






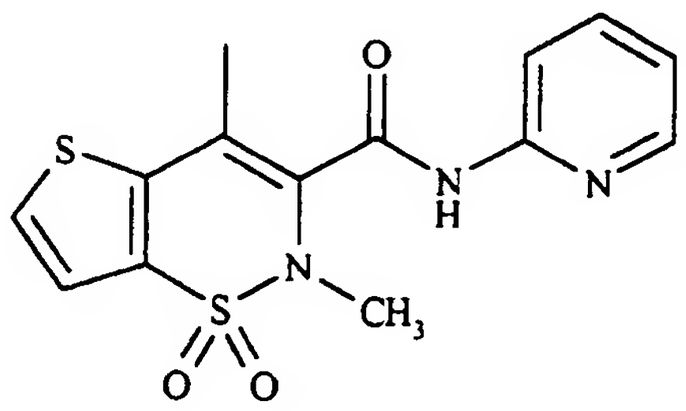


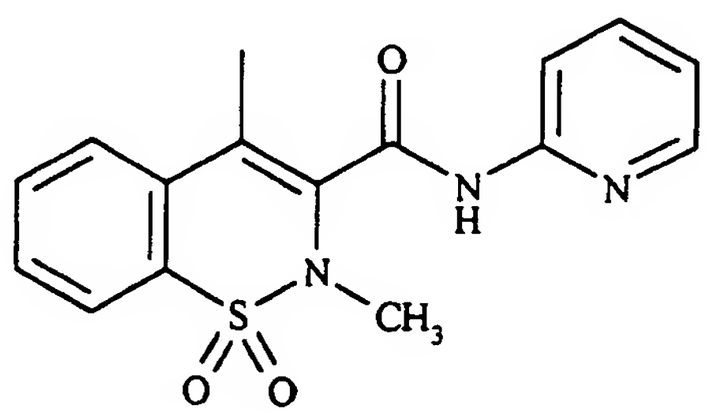


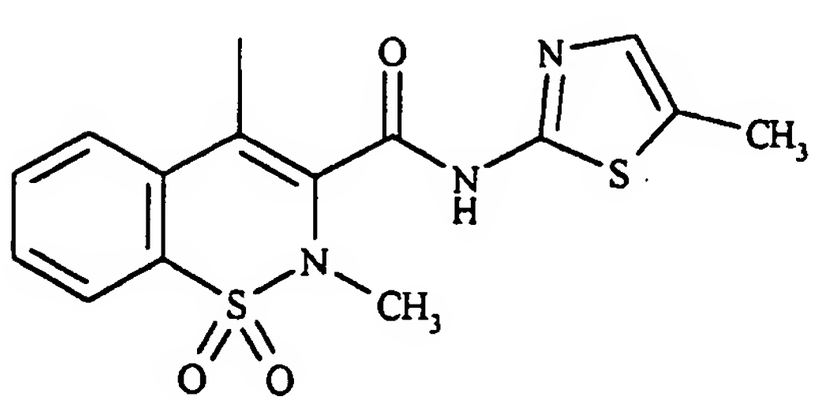


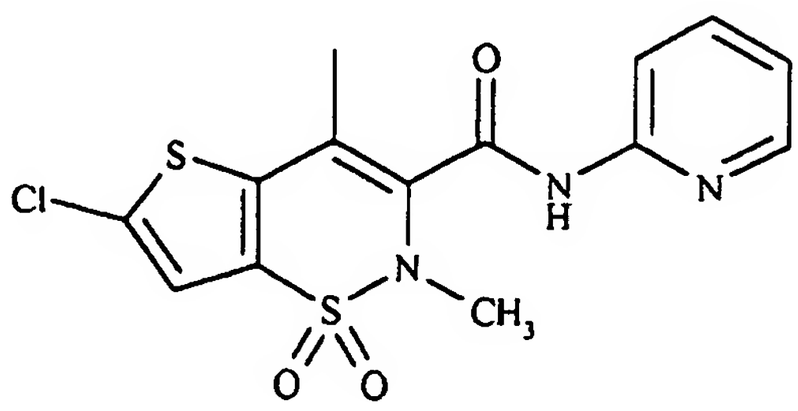
5

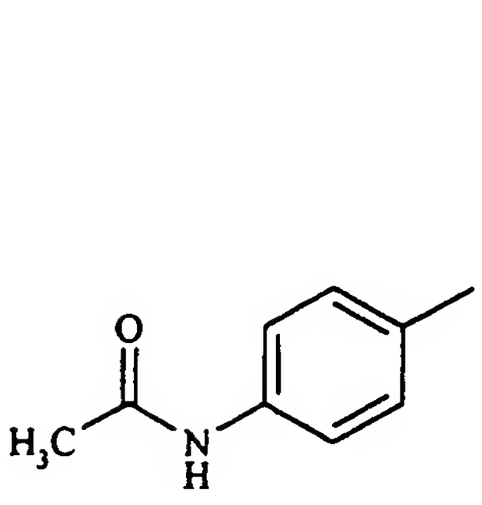
when **c** is equal to 0, **d** is equal to 0, $\mathbf{R^A}$ is selected from the group consisting of:

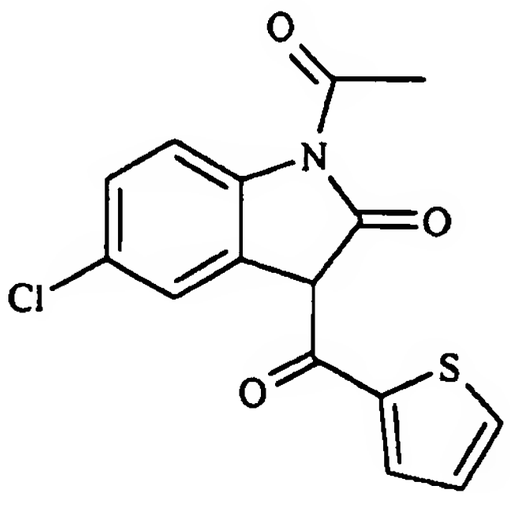






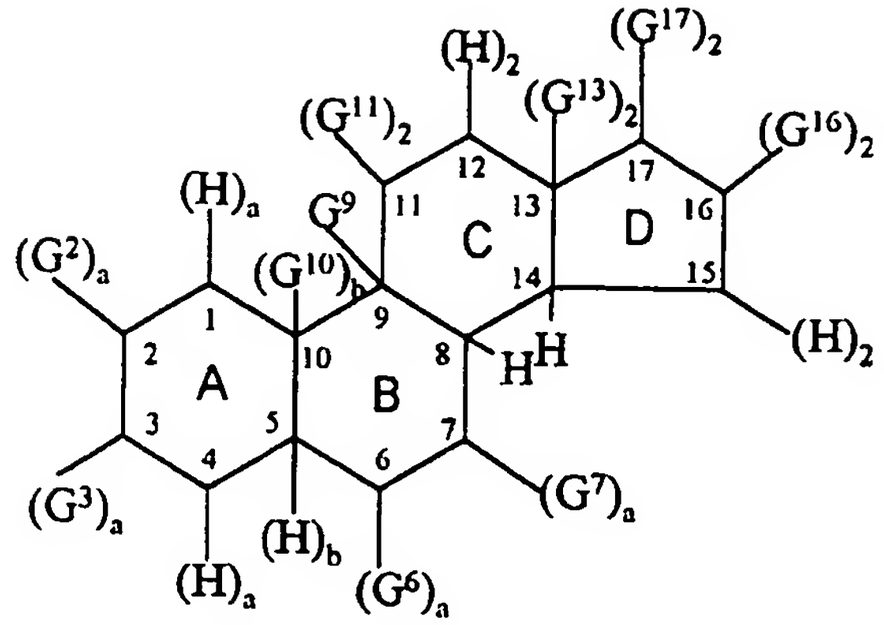






10

ii)



wherein:

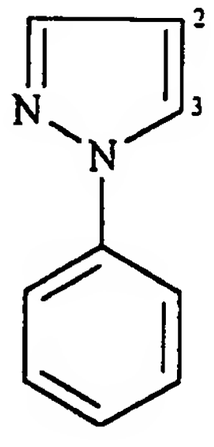
at the position 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 5-10 there may be a double bond; the ring A is optionally an aromatic ring;

a is equal to 1 or 2, **b** is equal to 0 or 1;

each G^2 is independently selected from the group consisting of H, Cl, Br;

each G^3 is independently selected from the group consisting of H, O-CH_3, O-CH_2-CH_2-Cl, OH; two G^3 can form a carbonyl group with the C^3 atom;

one G^2 and one G^3 can unite to form a ring of formula



wherein C^2=C^3 are part of the steroid structure;

each G^6 is independently selected from the group consisting of H, Cl, F, CH_3, -CHO;

each G^7 is independently selected from the group consisting of H, Cl, OH;

each G^9 is independently selected from the group consisting of H, Cl, F;

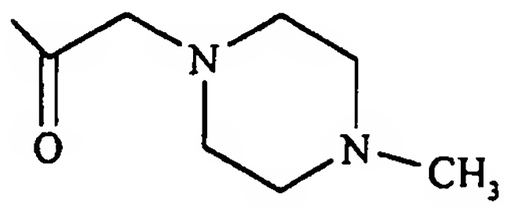
G^{10} is selected from the group consisting of H, Cl, F, CH_3, -CHO;

each G^{11} is independently selected from the group consisting of H, OH, , Cl; two G^{11} can form a carbonyl group with the C^{11} atom;

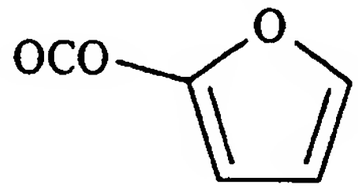
each G^{13} is independently selected from the group consisting of H, CH_3;

each G^{16} is independently selected from the group consisting of H, CH_3, OH; two G^{16} can form a vinyl group with the C^{16} atom;

each G^{17} is independently selected from the group consisting of H, OH and a monovalent radical comprising from 1 to 20 carbon atoms and from 0 to 5 oxygen, sulfur, nitrogen, halogen atoms; preferably it is H, OH, CH_3, C≡CH, CO-R-OH, CO-RH, CO-R-Cl, OCO-RH, CO-COO-RH, R-COOH, CH(OH)R-OH, COO-R-Cl, OC(O)O-RH, CO-R-SH, CO-R-O-CO-R-$N(CH_2CH_3)_2$, $CO-SCH_2F$, CO-R-OCORH,



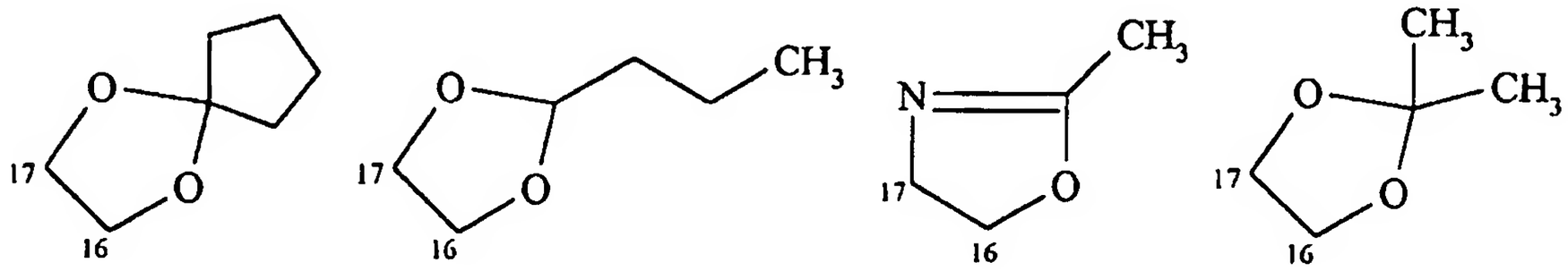
wherein R is a C_1-C_{20} linear or branched alkylene radical, and



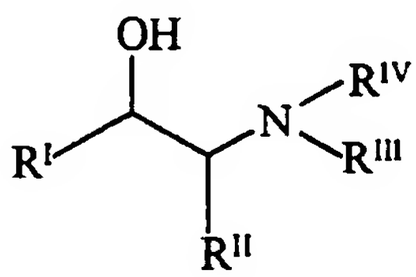
;

two G^{17} can form a carbonyl group with the C^{17} atom;

one G^{16} can unite with a G^{17} group to form, together with C^{16} and C^{17} the following groups:



iii)



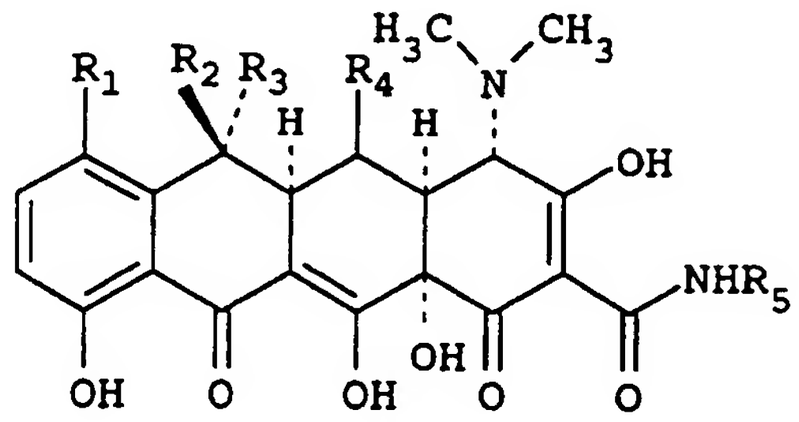
R^I is monovalent radical comprising from 6 to 20 carbon atoms and from 0 to 6 heteroatoms selected from oxygen, nitrogen, sulfur, chlorine, bromine, fluorine; examples of functional groups which are present in the radical R^I are the following: phenoxy, phenyl, thiazolyl, quinol-5-on-yl, pyridyl, tiofuranyl, tetrahydrofuranyl;

R^{II} is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms, preferably R^{II} is selected from the group consisting of H, CH_3 and CH_3CH_2

R^{III} is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms, preferably R^{III} is selected from the group consisting of H and CH_3;

R^{IV} is selected from the group consisting of hydrogen, a linear or branched alkyl having from 1 to 4 carbon atoms and a substituted aryl; preferably R^{IV} is selected from the group consisting of tert-butyl and isopropyl;

iv)



wherein:

R_1 is selected from the group consisting of H, Cl and dimethylamino,

R_2 is selected from the group consisting of H, OH,

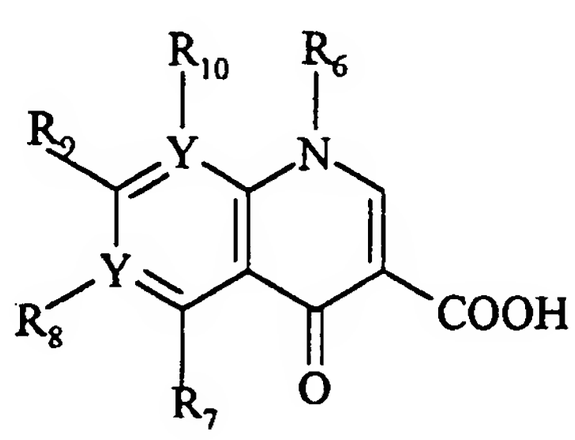
R_3 is selected from the group consisting of H, CH_3,

R_2 and R_3 together can be a methylene group (CH_2=),

R_4 is selected from the group consisting of H, OH,

R_5 is selected from the group consisting of H, CH_2OH and a monovalent radical containing from 5 to 20 carbon atoms and from 1 to 8 nitrogen atoms; the radical can further comprise other functional groups such as carboxyl and hydroxyl.

v)



wherein

each Y is independently selected from the group consisting of C and N,

R_6 is selected from the group consisting of cyclopropyl, phenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-fluoroethyl and ethyl;

R_7 is selected from the group consisting of H, amino, methyl,

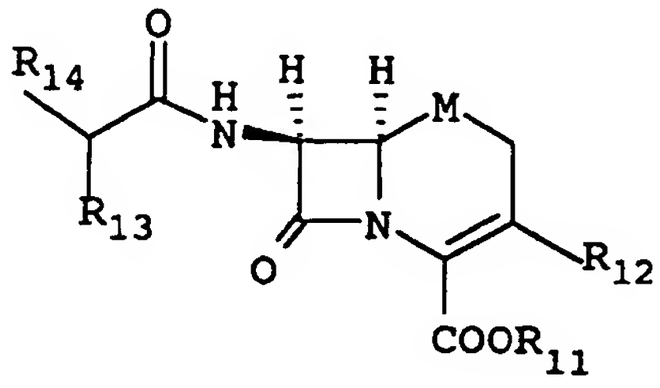
R_8 is selected from the group consisting of H and F;

R_9 is selected from the group consisting of H, methyl and a monovalent radical containing from 1 to 20 carbon atoms and from 1 to 4 nitrogen atoms;

R_{10} is selected from the group consisting of H, Cl and F;

R_6 e R_{10} can unite to form an optionally substituted six membered ring optionally containing up to two heteroatoms selected from the group consisting of oxygen and sulfur:

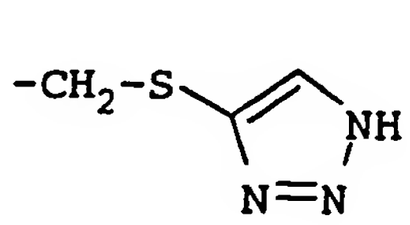
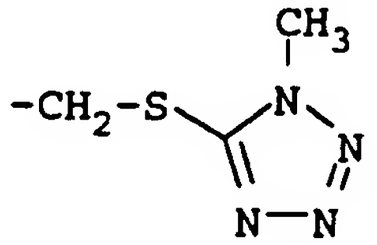
vi):



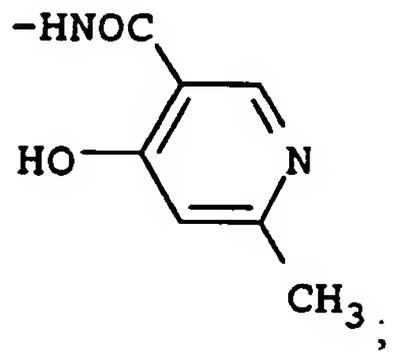
wherein

M is selected from the group consisting of sulfur, carbon or oxygen;

R_{11} is selected from the group consisting of H, pivaloyloxymethyl,

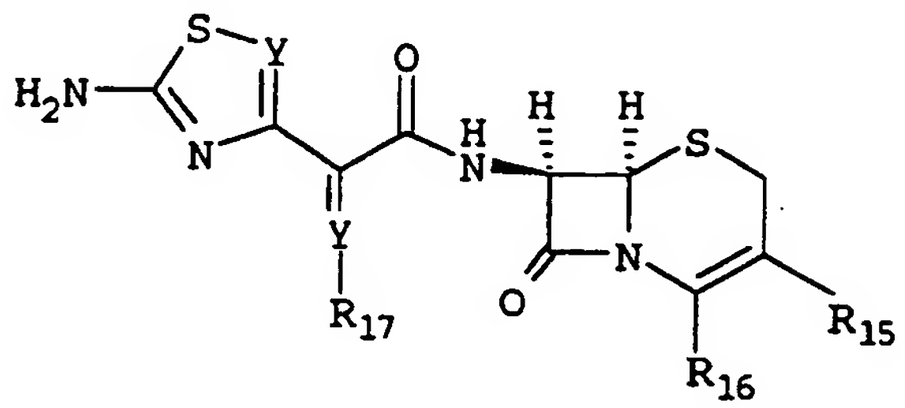
R_{12} is selected from the group consisting of chlorine and a monovalent radical containing from 1 to 5 carbon atoms, from 0 to 5 nitrogen atoms and from 0 to 1 sulfur atoms; preferably it is selected from chlorine, methyl, acetyloxymethyl, 2-propenyl  and  ;

R_{13} is selected from the group consisting of amino, hydroxyl and monovalent radical containing from 1 to 10 carbon atoms, from 0 to 5 oxygen atoms and from 0 to 5 nitrogen atoms;preferably it is selected from the group consisting of amino, hydroxyl, carboxyl and



R_{14} is an unsaturated C_6 ring, optionally substituted; preferably it is selected from the group consisting of phenyl, 1,4-cyclohexadienyl and 4-hydroxyphenyl.

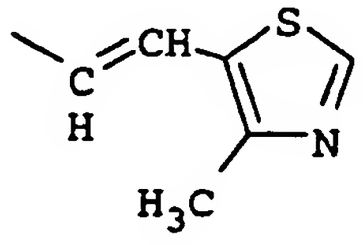
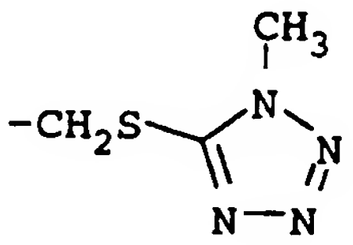
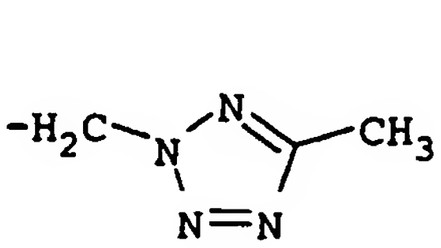
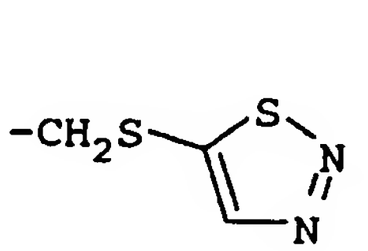
vii)



wherein:

each **Y** is independently selected from the group consisting of carbon and nitrogen

R_{15} is selected from the group consisting of hydrogen and a monovalent radical containing from 1 to 12 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms; preferably it is selected from the group consisting of H, methyl, ethyl, ethenyl, NH_2COOCH_2-, CH_3COOCH_2-, pyridilmethylene and


, 
, 
, 
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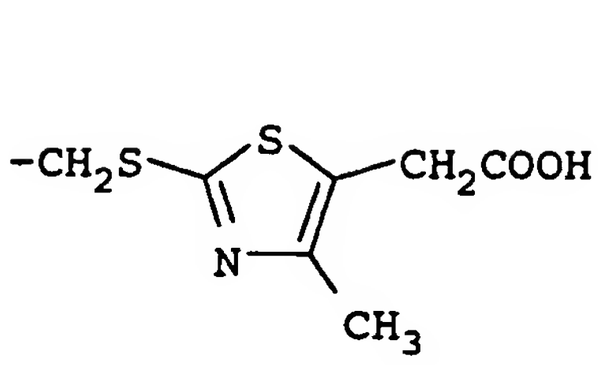
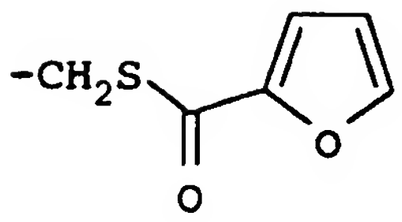
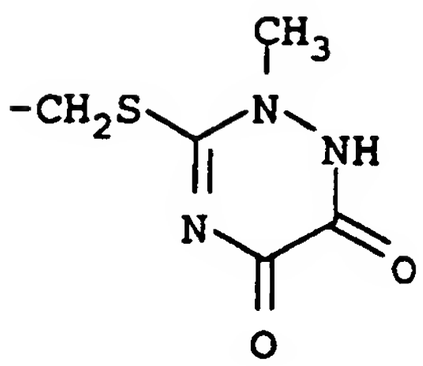
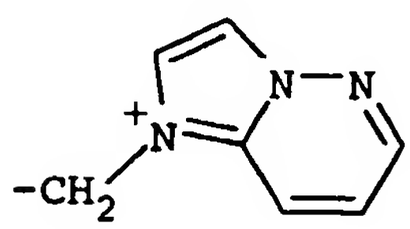
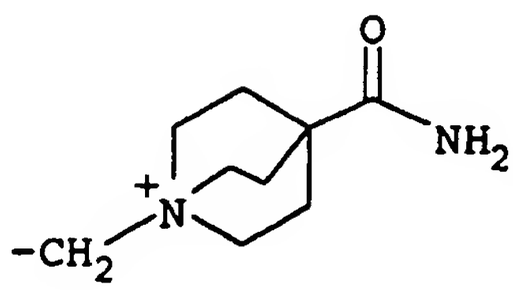
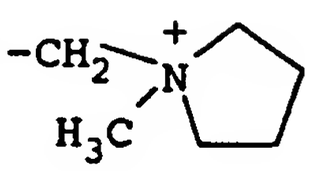
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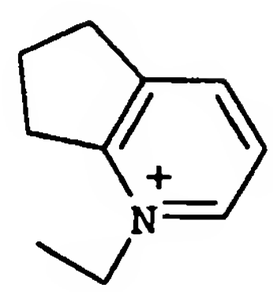
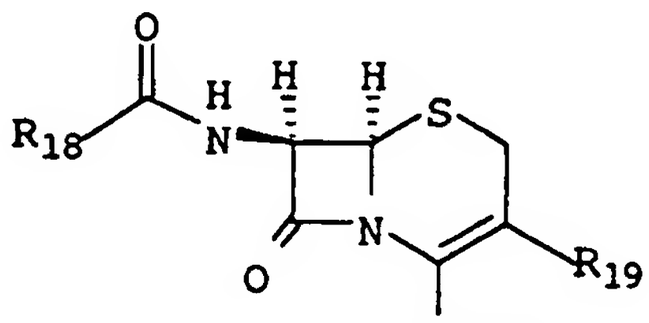

;

R_{16} is a monovalent radical containing from 1 to 10 carbon atoms and from 2 to 8 oxygen atoms; preferably it is selected from the group consisting of carboxyl, $(CH_3)_3CCOOCH_2OCO$- and $(CH_3)_2CHOCOOCH(CH_3)OCO$-; when R_{15} is a quaternary ammonium cation, R_{16} is optionally a $-COO^-$;

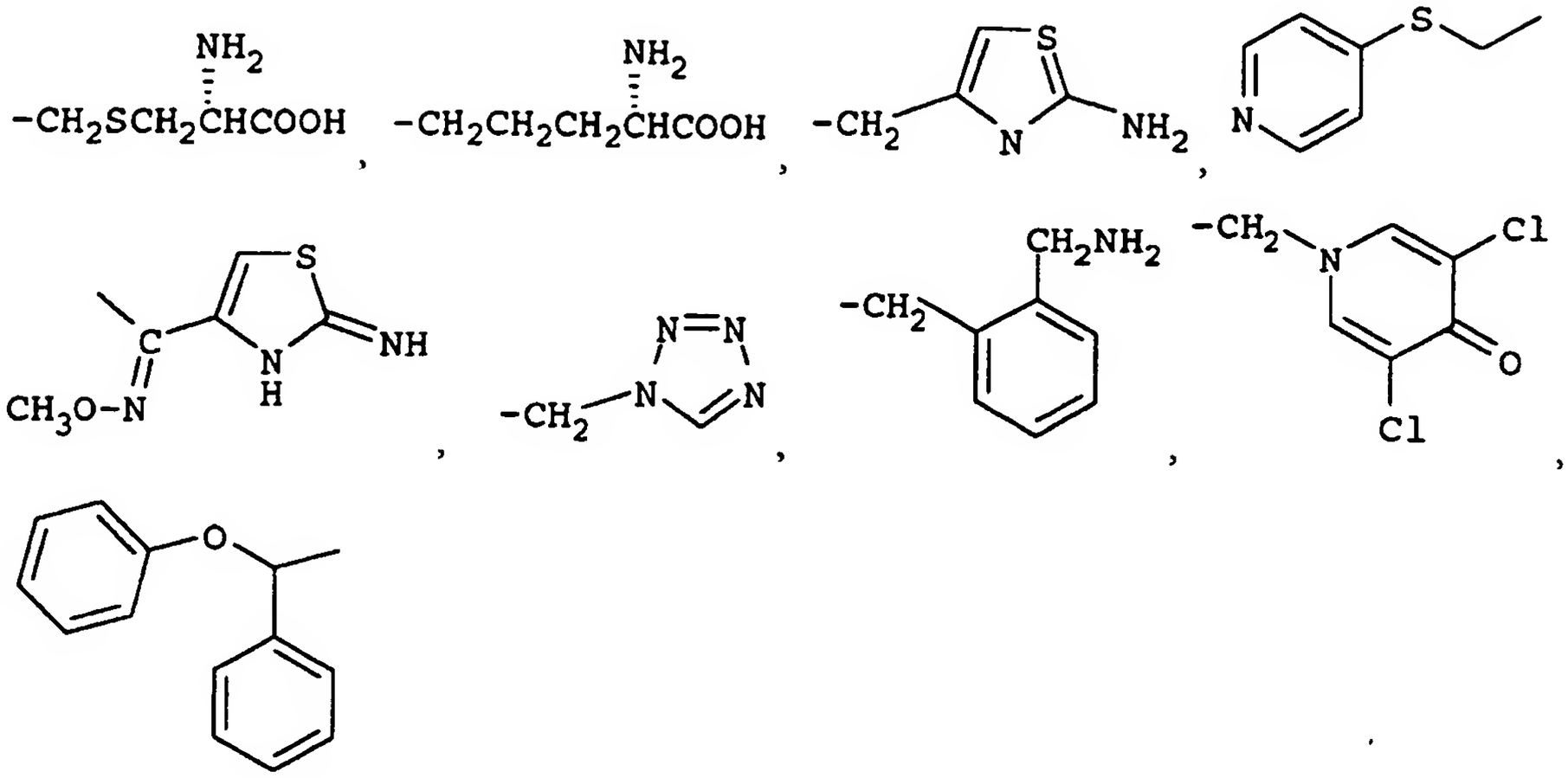
R_{17} is selected from the group consisting of -OH and a monovalent radical containing from 1 to 12 carbon atoms and from 0 to 4 oxygen atoms, preferably it is selected from the group consisting of -OH, $-OCH_3$, $-CH_2CH_3$, $-OCH_2COOH$, $-CH_2COOH$, $OC(CH_2)_3$-COOH.

viii)

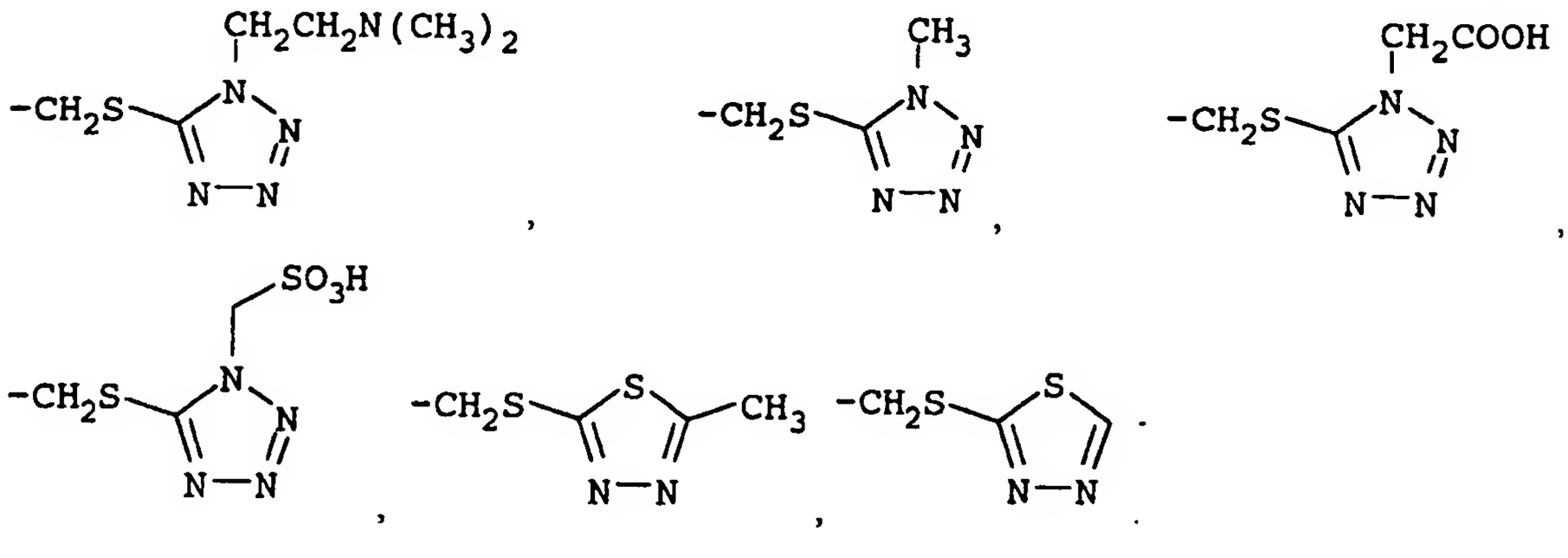


wherein:

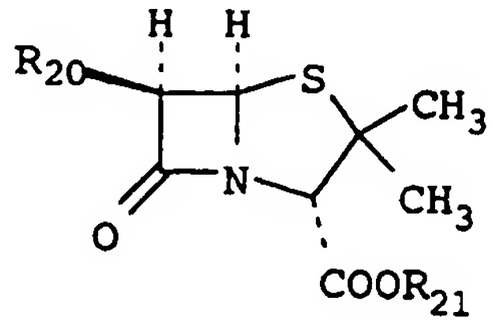
R_{18} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms; preferably it is selected from the group consisting of: PhCH(OH)-, $-CH_2CN$



R_{19} is selected from the group consisting of H and a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 6 nitrogen atoms and from 0 to 3 sulfur atoms; preferably it is selected from the group consisting of: CH_3COOCH_2,

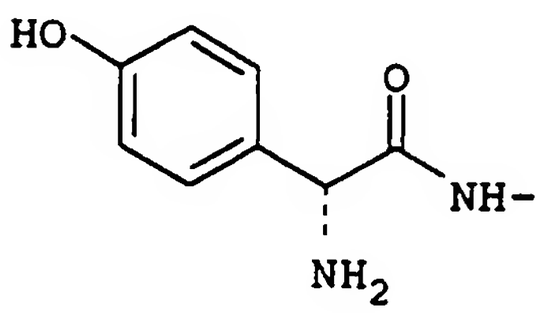


ix)



wherein:

R_{20} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms, from 0 to 3 fluorine atoms and from 0 to 3 chlorine atoms; preferably it is selected from the group consisting of: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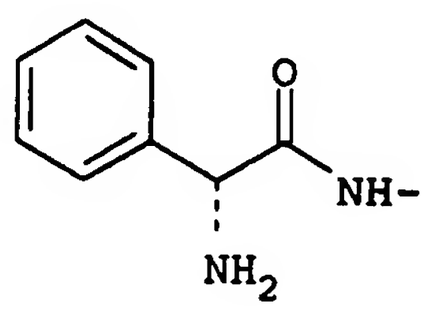
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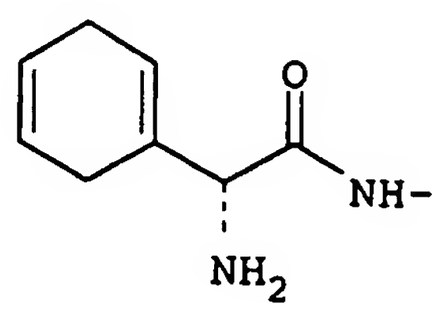
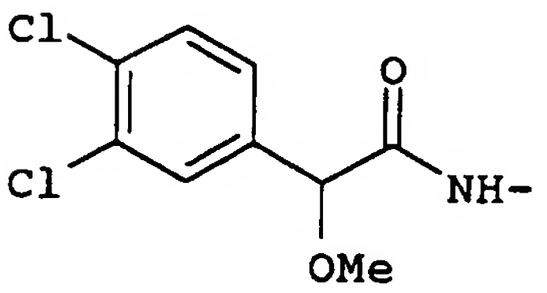
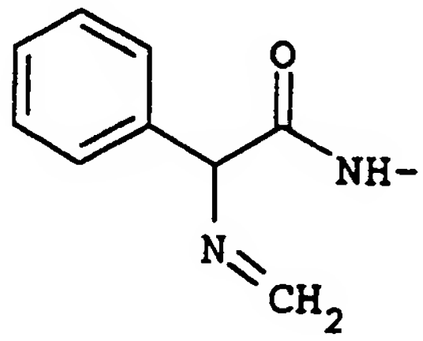

,


,

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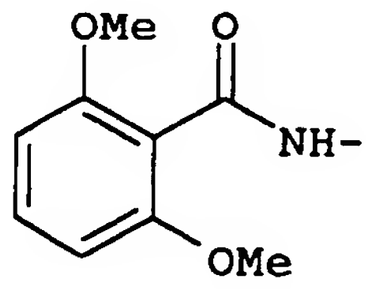
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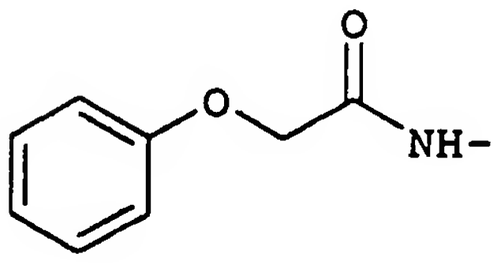
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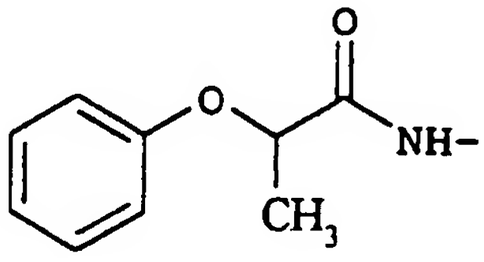
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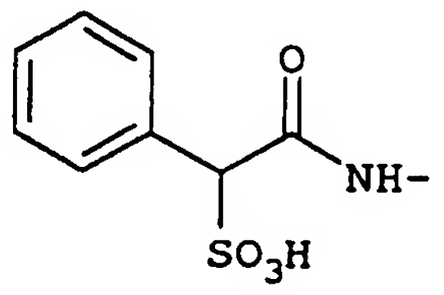
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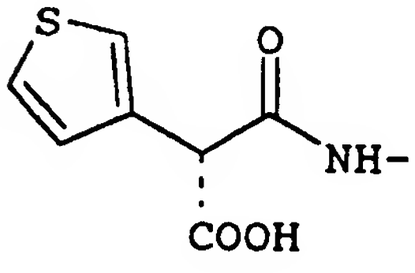

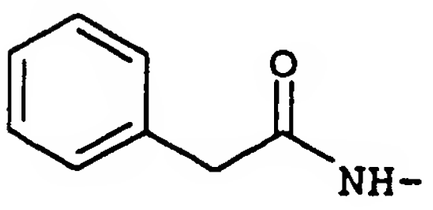
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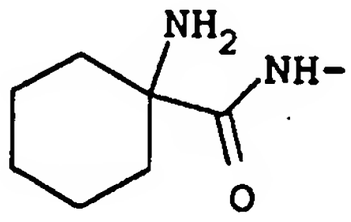
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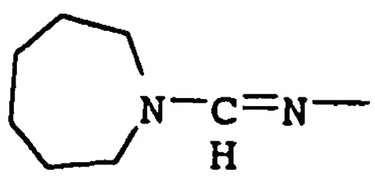
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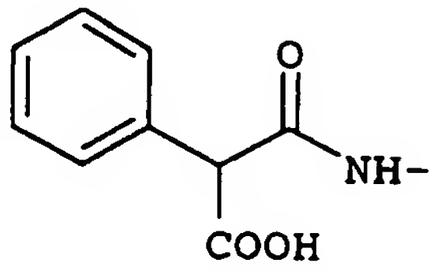
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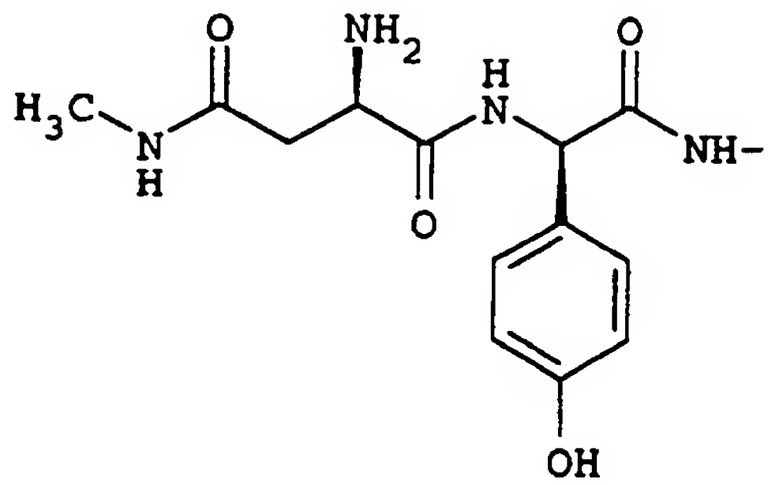
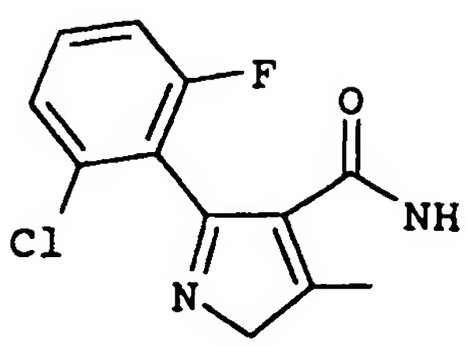
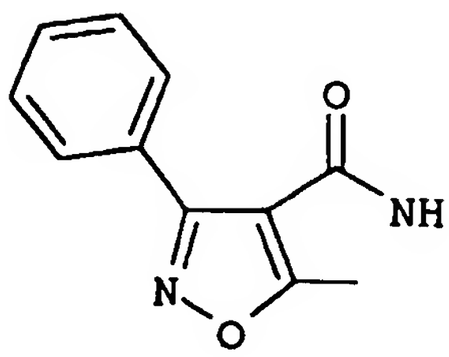
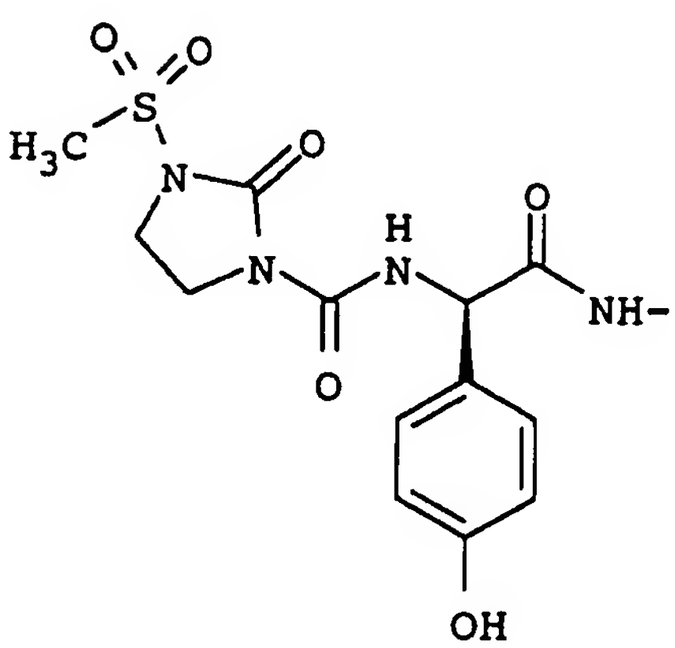
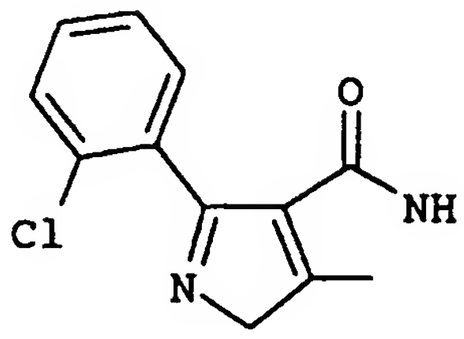
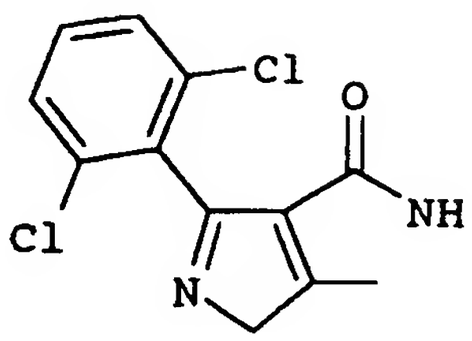
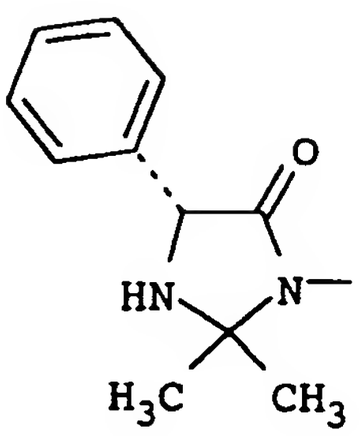
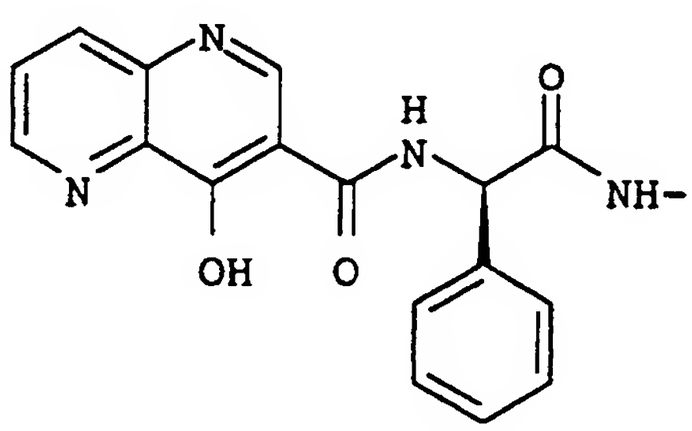
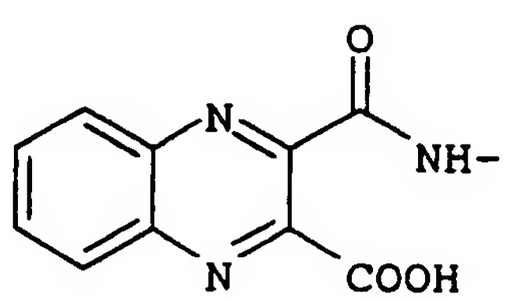
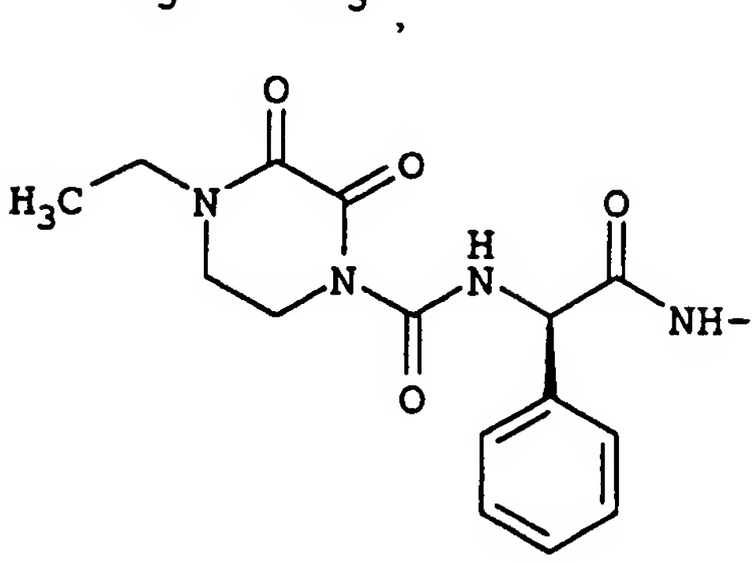

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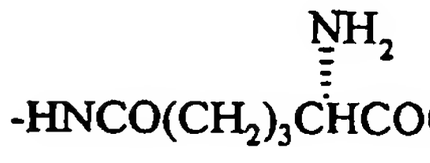
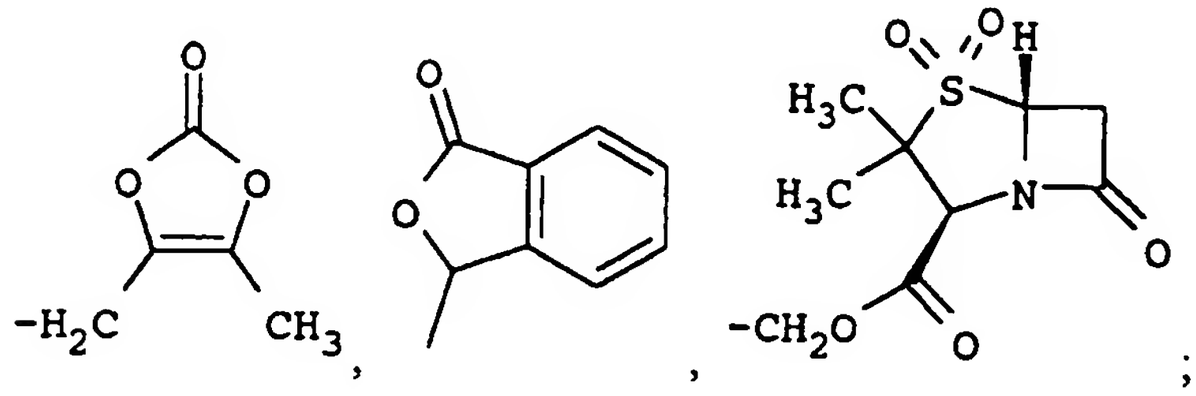

, -NHCO(CH$_2$)$_3$CH(NH$_2$)COOH, CH$_2$=CH$_2$SCH$_2$CONH-;

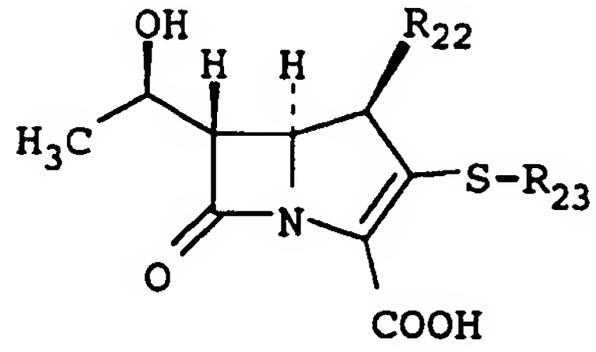
R_{21} is selected from the group consisting of H and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms and

from 0 to 3 sulfur atoms; preferably it is selected from the group consisting of: H, -$CH_2OCOC(CH_3)_3$, -$CH(CH_3)OCOOC_2H_5$, -$CH_2CH_2N(CH_2CH_3)_2$,



;

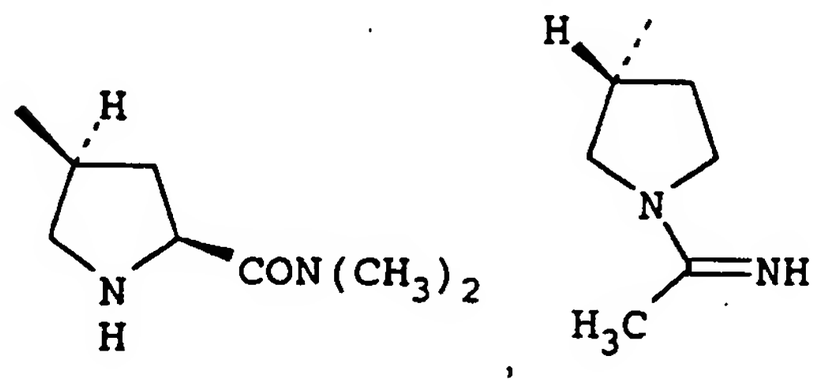
x)



wherein:

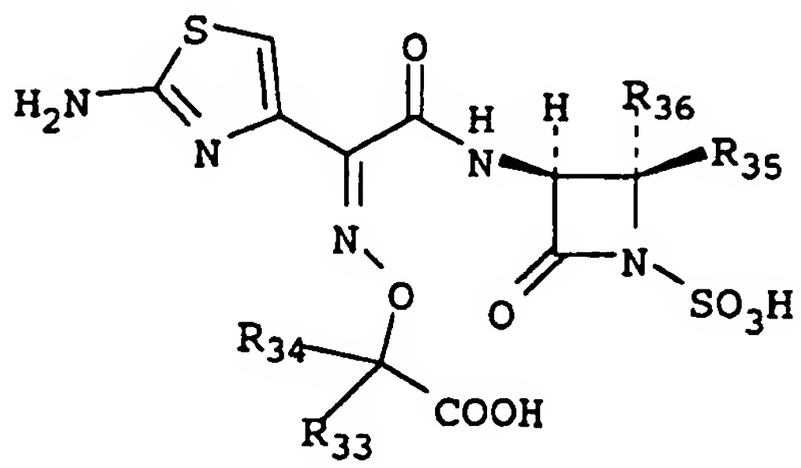
R_{22} is selected from the group consisting of H and methyl;

R_{23} a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms and from 1 to 5 nitrogen atoms; preferably it is selected from the group consisting of: -$CH_2CH_2NHCH=NH$,



,

xi)

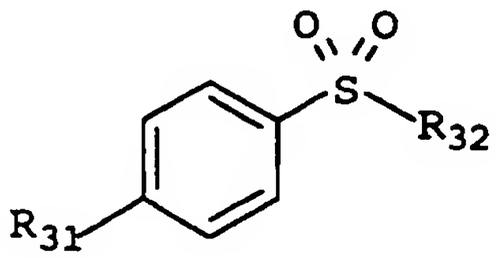


wherein:

R_{33} , R_{34} and R_{36} are independently selected from the group consisting of H and CH_3;

R_{35} is selected from the group consisting of H and $-CH_2OCONH_2$,

xii)



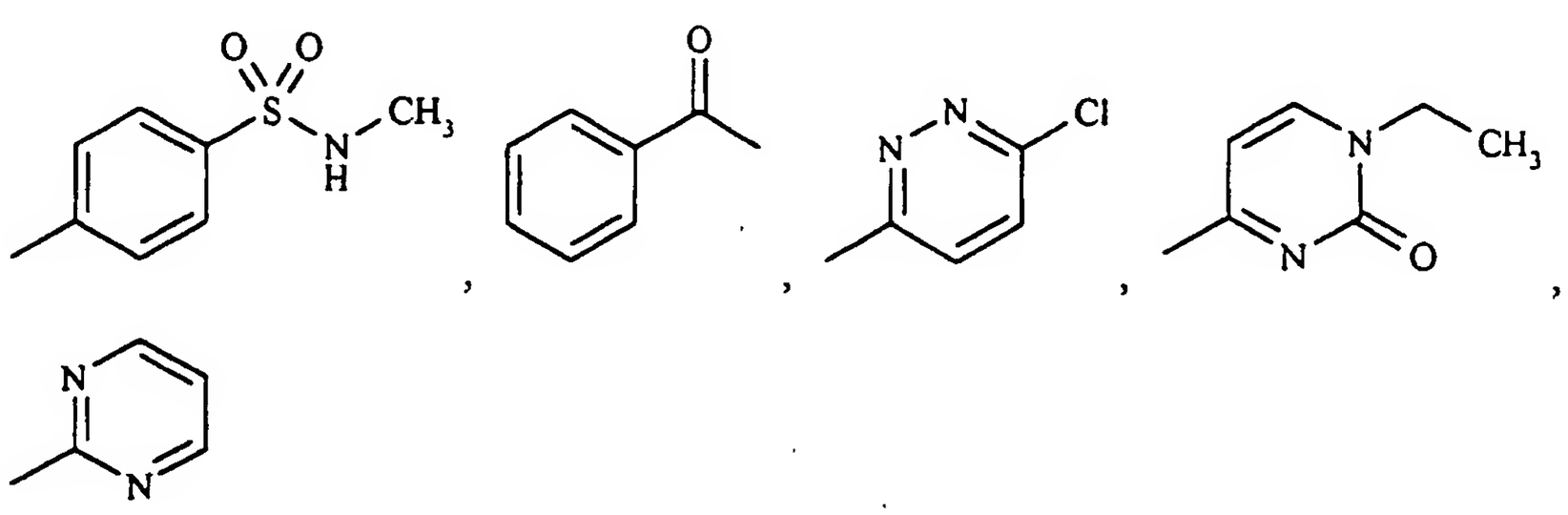
wherein:

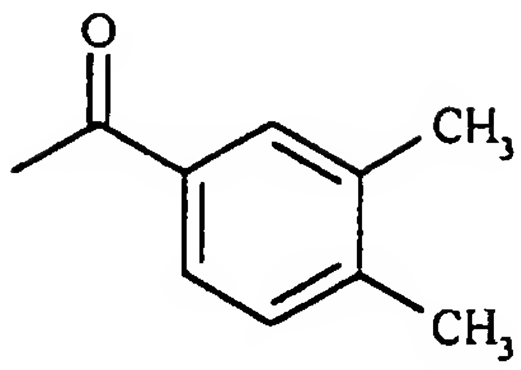
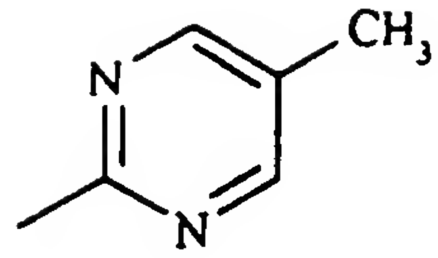
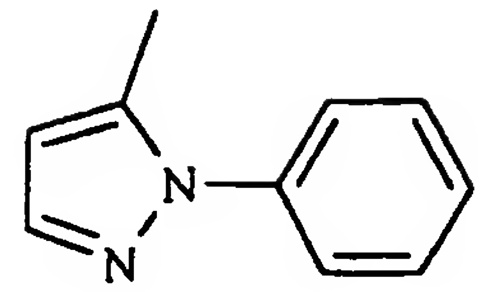
R_{31} is selected from the group consisting of $-NH_2$, $-CH_2NH_2$ and $-NHCH_2Ph$

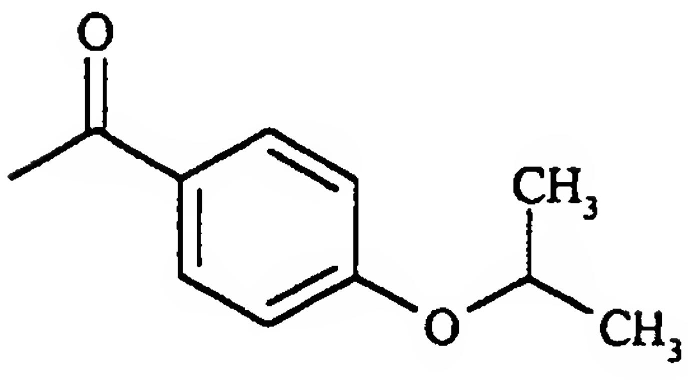
R_{32} is selected from the group consisting of $-NH_2$, $-NHR_{26}$ and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 5 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms; wherein R_{26} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms;

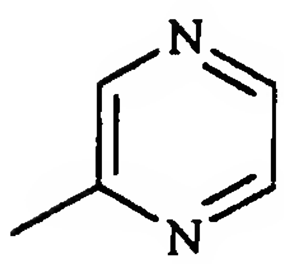
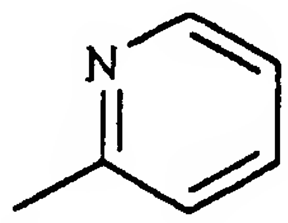
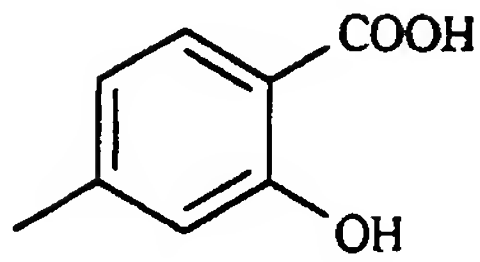
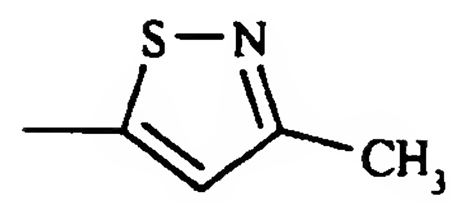
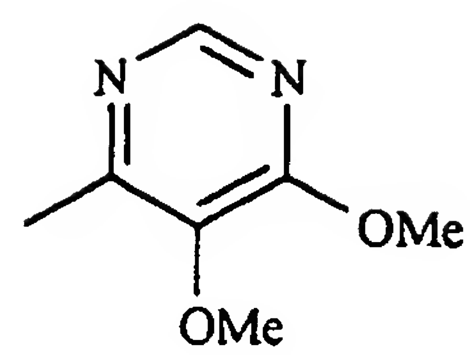
preferably R_{32} is selected from the group consisting of: 4-(2-hydroxyethylamino)phenyl, guanyl, 4-(amino)phenyl, 4-(aminomethyl)phenyl, 4-(carboxymethylamino)phenyl, succinylaminophenyl, 2-amino-5-thiazolyl;

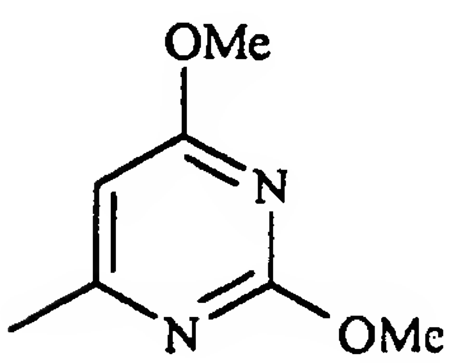
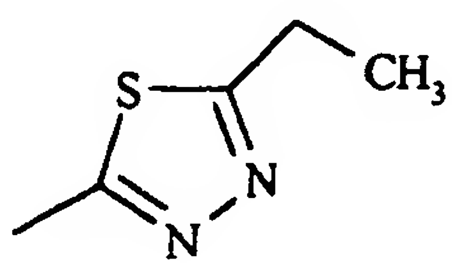
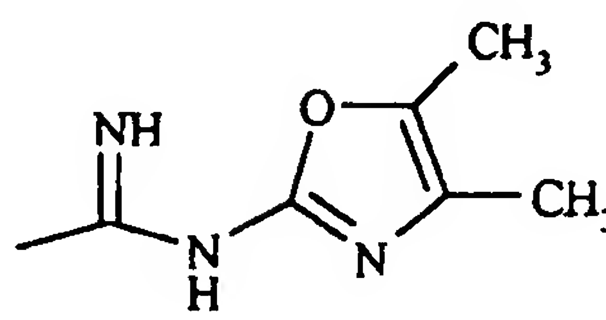
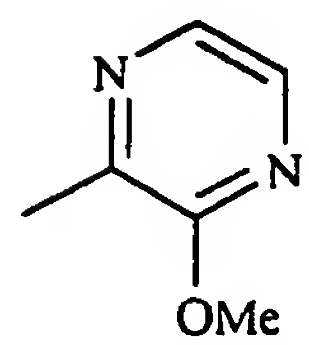
preferred examples of R_{26} are: acetyl, carbamoyl, 3-methyl-2-butenoyl, aminothioxomethylene,

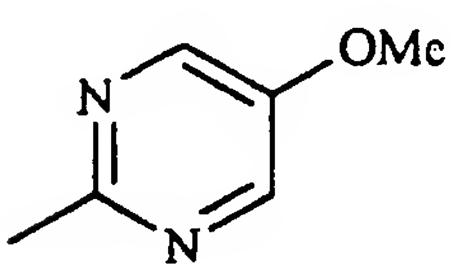
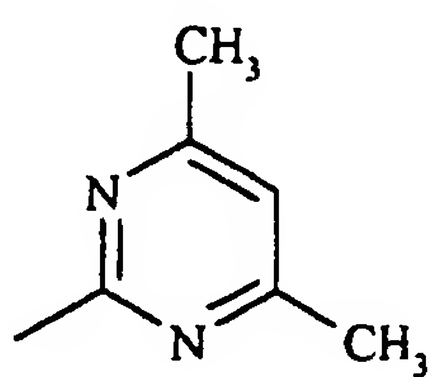
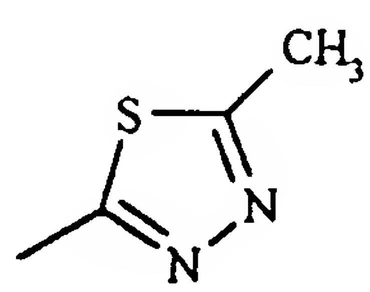
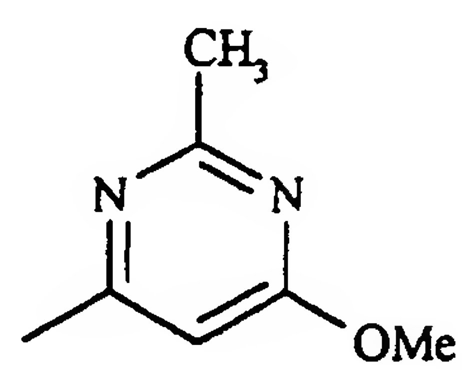


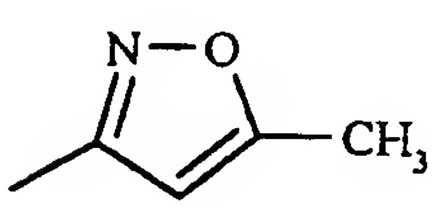
 ,
 ,
 ,

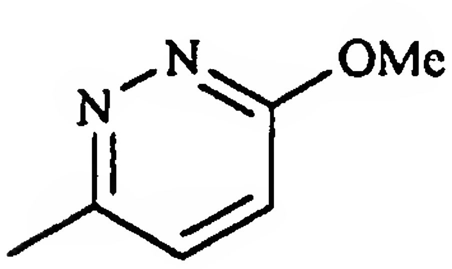
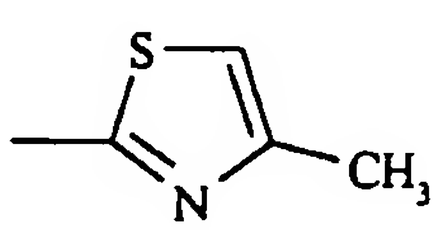
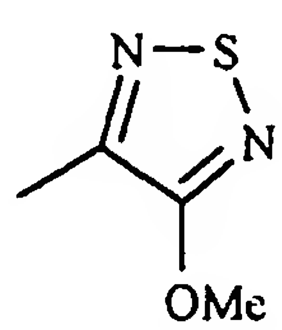
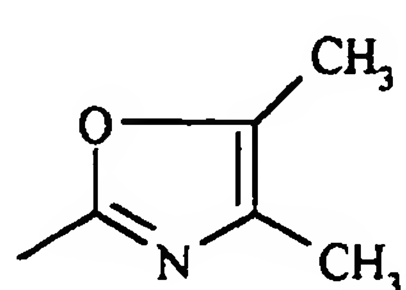
 ,

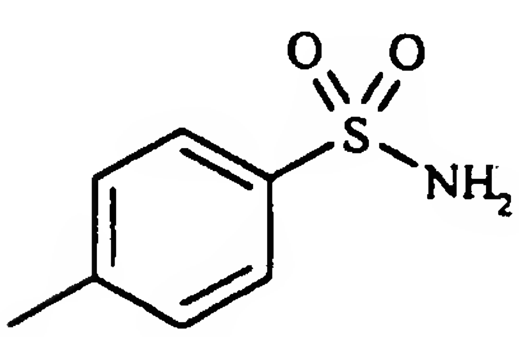
 ,
 ,
 ,
 ,
 ,

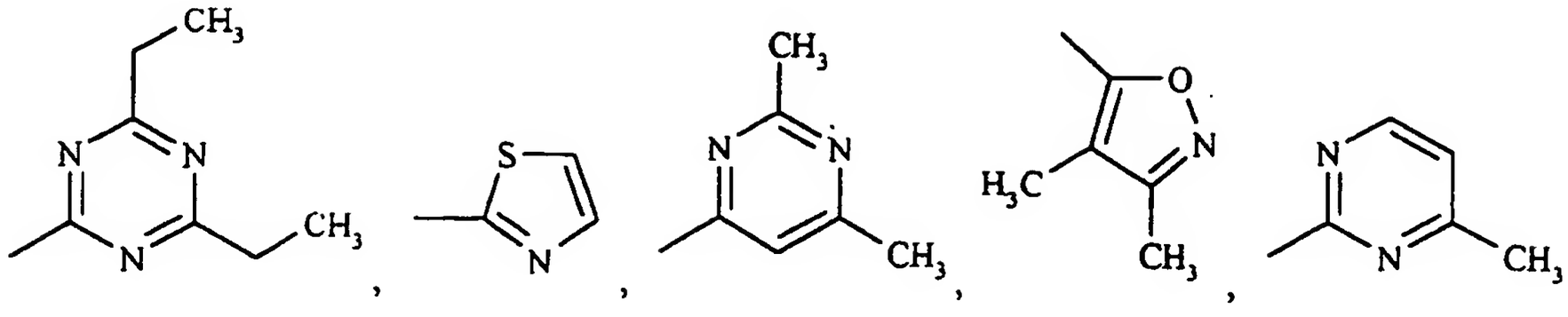
 ,
 ,
 ,
 ,

 ,
 ,
 ,
 ,

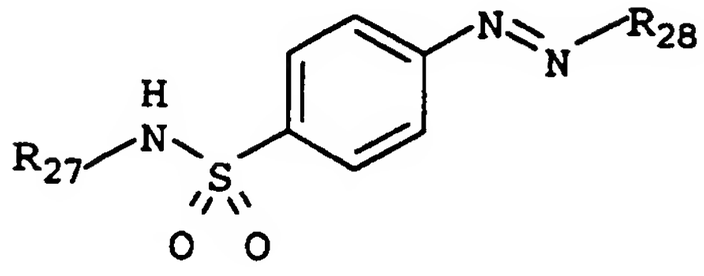
 ,

 ,
 ,
 ,
 ,

 ,



xiii)

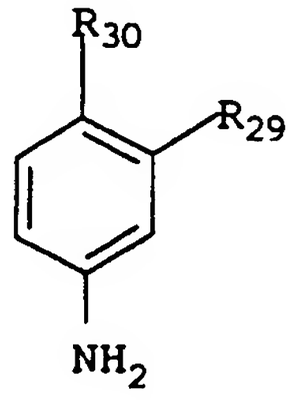


wherein:

R_{27} is selected from the group consisting of H and 4,6-dimethyl-2-pyrimidinyl;

R_{28} is a phenyl group substituted in at least 2 of the positions 2, 3, 4 and 6 by a group selected from hydroxyl, carboxyl and amino; preferred examples of R_{28} are 2,4-diamino-6-carboxyphenyl, 2,4-diaminophenyl, 3-carboxy-4-hydroxyphenyl;

xiv)



wherein:

R_{29} is selected from the group consisting of hydrogen and hydroxyl

R_{30} is selected from the group consisting of carboxyl, phenoxycarbonyl, 4-(amino)phenylsulfinyl, hydrazinocarbonyl;

xv)